Synthesis of DEFG ring system of cneorins

Ari M. P. Koskinen* and Ainoliisa J. Pihko

Laboratory of Organic Chemistry, Department of Chemistry, Helsinki University of Technology, PO Box 6100, FI-02015 TKK, Finland
E-mail: ari.koskinen@tkk.fi

Abstract
The cneorins have been isolated from the xerophytic shrub *Cneorum pulverulentum*, which is native to the Canary Islands. They are natural products containing a [4.3.1]propellane ring system (DEFG rings) as the northern part of the molecule and a 5,5-spiroketal unit and a butenolide moiety (A ring) as the southern part. The synthesis of the DEFG ring system of the cneorins is described. The key steps include: intramolecular cyclopropanation of a diazomalonate providing the EFG ring fragment and an anionic cyclization of a sulfone yielding the [4.3.1]propellane ring system.

Keywords: Total synthesis, natural products, cneorins, intramolecular cyclopropanation of diazomalonates

Introduction

The cneorins (**1**, **2**) (Figure 1) were originally isolated from the xerophytic shrub *Cneorum pulverulentum*, native to the Canary Islands, in the late 1970's.[1] This shrub hosts a variety of bitter principles, all of which contain the [4.3.1]propellane ring system.[2] These oxidized pentanortriterpenes (C_{25} compounds) also have other interesting structural features in common, such as a 5,5-spiroketal unit and a butenolide moiety. The relative stereochemistry of the parent natural products were initially reported based on degradation studies, and later confirmed by X-ray diffraction structures. The absolute stereochemistry has been indirectly determined for only one derivative of cneorin C, and must be considered with caution for the other structural members of these natural products. Biogenetically these compounds are thought to be related to the limonoid triterpenes.[3] Due to lack of material from natural sources, these compounds have not received proper pharmacological screening. In addition to *Cneorum pulverulentum*, the Cneoraceae plant family consists of two other species, *Cneorum tricoccon*, which is native to coastal areas of the western Mediterranean, and *Cneorum trimerum*, which belongs to the flora of

Cuba. The tricoccins (**3**, Figure 1) were isolated from the former, but the latter has not been adequately studied due to lack of access to the required plant materials. Recently, some close structural relatives of the cneorins, the cedkathryns (**4**), were isolated from *Cedrelopsis gracilis* from Madagascar (Figure 1).[4] In addition, some compounds that could result from rearrangements of the cneorins or the tricoccins, for example cedmilinol (**5**), have been isolated from *Cedrelopsis grevei*.[5]

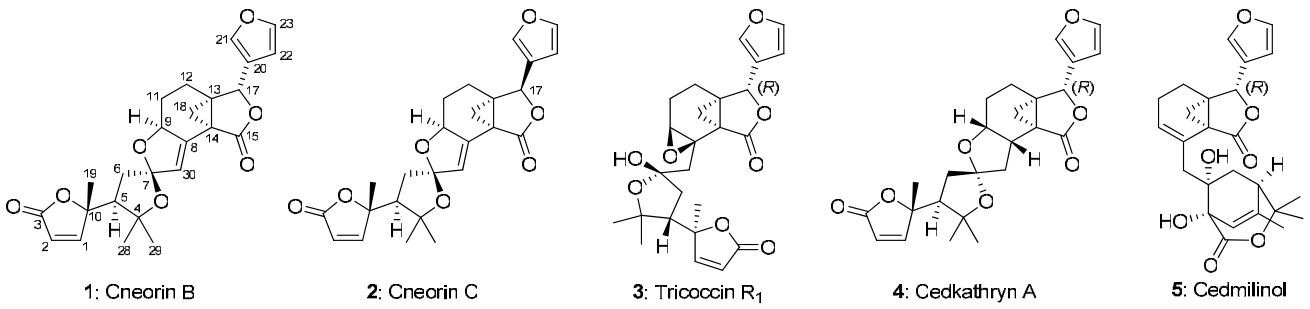
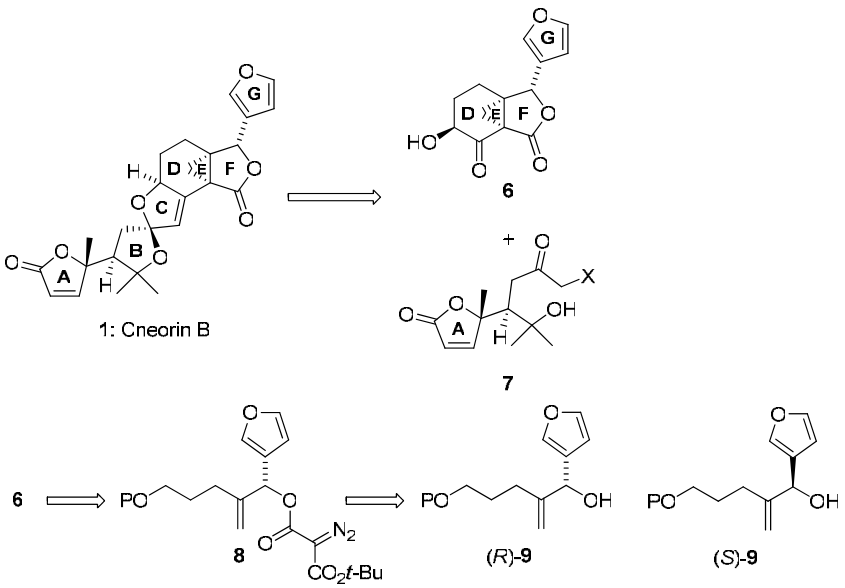


Figure 1. Selected structures of natural products related to cneorins.

Despite the intriguing structures of the cneorins, these molecules have not attracted synthetic attention except from our group.[6] Retrosynthetically (Scheme 1), the structure of cneorin C can be divided into two advanced substructures, namely hydroxyketone **6**, which consists of the DEFG rings of the molecule, and the A ring butenolide fragment **7**. The DEFG ring system of cneorin B (**6**) is an ideal candidate for the intramolecular cyclopropanation[7-11] of diazomalonate **8**, which can be conveniently prepared from the furyl substituted allylic alcohol (*S*)-**9**.

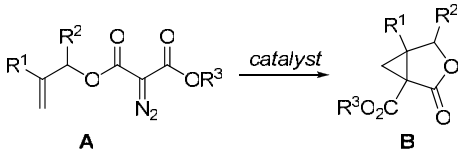


Scheme 1. Retrosynthetic analysis of cneorin B.

We have previously described the enantioselective synthesis of allylic alcohol (*S*)-**9** by enzymatic kinetic resolution.[6] In this paper we disclose our results on the cyclopropanation to yield the EFG ring fragment and closing the D ring to obtain the [4.3.1]propellane structure of cneorin related natural products.

Results and Discussion

Transition metal catalyzed intramolecular cyclopropanation reactions have been reviewed.[10] Some mechanistic studies of the intermolecular copper(I)-catalyzed cyclopropanations have also been published.[12-14] The intramolecular cyclopropanation of diazomalonates of type **A** in Scheme 2 (a 1,1-disubstituted olefin) is unprecedented in the literature, although there are earlier examples of both 1,2-disubstituted and even 1,2,2–trisubstituted olefins being cyclopropanated with copper catalysts.[8]



Scheme 2. Intramolecular cyclopropanation of a diazomalonate.

The catalyst complexes (Figure 2) and reaction conditions used in this study were chosen in accordance with earlier results,[9-11] according to which the best results were obtained with catalyst complex **10c**.[15] The air stability and ease of handling of $Cu(MeCN)_4PF_6$[16] was reported to make the PF_6 salts superior to CuOTf.[17] We therefore decided to investigate also complexes **10a** and **10b**[18] the latter of which was expected to exhibit reduced Lewis acidity of copper thus making it less reactive and more selective towards the targeted double bond.

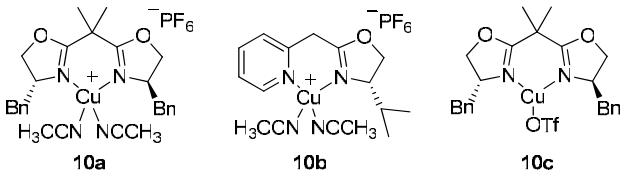
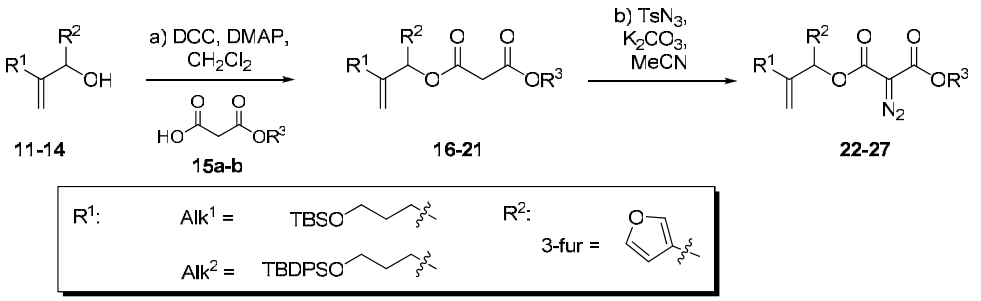


Figure 2. Catalysts employed in the intramolecular cyclopropanation.

The diazomalonates for the cyclopropanation reaction were synthesized as follows (Scheme 3 and Table 1). Alcohols **11-14** were treated with the monoester of malonic acid **15a-b** in the presence of dicyclohexylcarbodiimide and DMAP[19] to provide the corresponding malonates **16-**

21. Diazo transfer[20] of the malonates with tosyl azide[21] gave the cyclopropanation precursors **22-27**.



Scheme 3. Synthesis of diazomalonates. For substrates and yields, see Table 1.

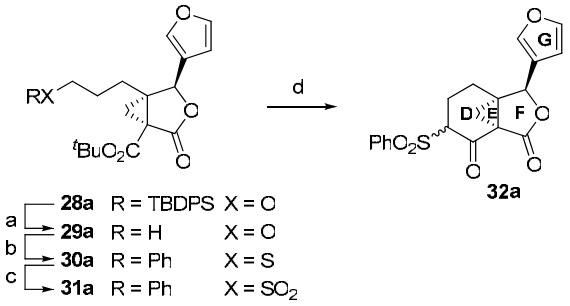
Table 1. Substrates and yields for preparation of the diazomalonates (see Scheme 3)

Entry	Alcohol	R^1	R^2	Malonic acid	R^3	Malonate	Yield step a	Diazo-malonate	Yield step b
1	**11**	Me	Ph	**15a**	Et	**16**	63 %	**22**	quant.[a]
2	**12**	Me	3-fur	**15a**	Et	**17**	67 %	**23**	71 %
3	**13**	Alk^1	3-fur	**15a**	Et	**18**	81 %	**24**	92 %
4	**13**	Alk^1	3-fur	**15b**	*t*-Bu	**19**	88 %	**25**	93 %
5	**14**	Alk^2	3-fur	**15a**	Et	**20**	97 %	**26**	quant.[a]
6	**14**	Alk^2	3-fur	**15b**	*t*-Bu	**21**	98 %[a]	**27**	98 %

[a]Crude yield.

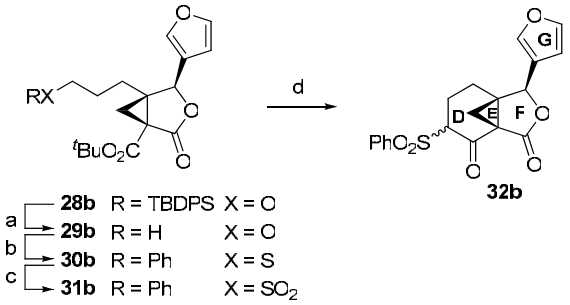
The ability of the furan ring to participate in carbenoid insertion reactions is well known,[22,23] and indeed, the model studies confirmed this. Whereas in a model study, the phenyl substituted diazomalonate **22** upon treatment with catalyst **10c** produced the corresponding cyclopropanolactone in 67% yield, the 3-furyl substituted diazomalonates were extensively decomposed with this catalyst. We soon learned that for the alcohol protection, TBS was too labile, and the ethyl allyl malonates also led to extensive decomposition. Finally, of the examined Cu catalyst complexes, **10a** gave reproducible cyclopropanation of **27** to give **28** in 30% yield as a separable 1:1 mixture of diastereomers.

Thus, we embarked on the synthesis of both the *anti*- and *syn*-diastereomers of ketosulfone **32** with the *t*-butyl ester. The TBDPS protected *anti*-cyclopropanolactone **28a** was deprotected with tetrabutylammonium fluoride[24] to yield alcohol **29a** in modest yield (Scheme 4), which was then transformed into sulfide **30a** under the Hata conditions[25,26] and the sulfide was oxidized with *m*-CPBA to sulfone **31a** in excellent yield. Exposure of sulfone **31a** to *n*-BuLi in THF at –100 °C gave the [4.3.1]propellane **32a** in 55% yield as a 1:0.8 mixture of two diastereomers at the sulfur bearing carbon.



Scheme 4. (a) TBAF, THF, 0 °C → rt, 2 h, 57%; (b) $(SPh)_2$, Bu_3P, pyr, 0 °C → rt, 1.5 h, 75%; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 1 h, 88%; (d) *n*-BuLi, THF, –100 °C, 30 min, 55%.

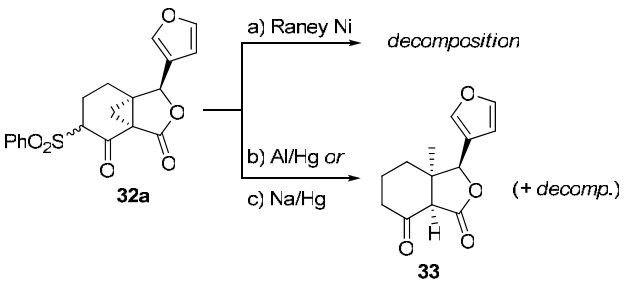
In the diastereomeric series towards cneorin B and the other natural products shown in Figure 1, the synthesis proceeded similarly, except for the closure of ring D. With the *syn*-phenylsulfone **31b**, *n*-BuLi did not only affect the D ring cyclization but the *n*-butyl anion attacked the lactone as well. Fortunately, subjecting sulfone **31b** to KHMDS provided the cyclized product.



Scheme 5. (a) TBAF, THF, 0 °C → rt, 3 h, 80%; (b) $(SPh)_2$, Bu_3P, pyr, 0 °C → rt, 2.5 h, 65%; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h, 80%; (d) KHMDS, THF, –100 °C, 1 h, 36% based on recovered **31b**.

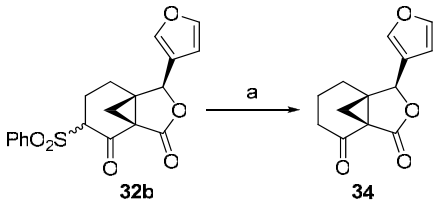
Having secured access to the DEFG ring system, we considered different options for removing the sulfone from **32**. Single electron reductants such as Raney Ni, Na/Hg and Al/Hg have traditionally been used to reduce the sulfur – carbon bond. Reductive opening of cyclopropyl ring systems conjugated to carbonyl groups with single electron reductants is also known in the literature.[27-30]

Results of the sulfone removal of the *anti*-diastereomer are presented in Scheme 6. Raney nickel caused slow decomposition of the starting sulfone **32a** and the other single electron reductants, aluminum amalgam[31] and sodium amalgam,[32] effected a reductive opening of the cyclopropyl ring and ketone **33** was obtained in addition to decomposed starting material.[33]



Scheme 6. (a) Raney Ni, EtOH, THF, rt, 18 h; (b) Al-foil immersed in aq. $HgCl_2$,[33] THF:H_2O 9:1, 0 °C → rt (slowly), 4 h, 45%; (c) Na-Hg, Na_2HPO_4, THF, MeOH, –15 °C → rt (slowly), 4 h, yield not determined.

Undeterred by the results with the *anti*-diastereomer **32a**, we submitted the *syn*-diastereomer **32b** to the aluminum amalgam reduction, which to our delight produced ketone **34** (Scheme 7).



Scheme 7. (a) Al-foil immersed in aq. $HgCl_2$,[33] THF:H_2O 9:1, 0 °C → rt, 3 h, 40%.

Summary

In this work, the synthetic efforts towards the DEFG ring system of cneorin B and C have been reported. Synthesis of cneorin C was hampered by difficulties in removing the sulfone from *anti*-ketosulfone **32a**. Fortunately, this step was successful for the *syn*-diastereomer **32b**.

The enantiomer of the DEFG ring fragment of cneorin B **34** was synthesized for the first time in 14 steps from commercially available starting materials. This is the first time that a cyclopropane containing [*n.n.*1]propellane structure of a natural product has been prepared by means of a cyclopropanation reaction.

Experimental Section

1-Furan-3-yl-2-methylprop-2-en-1-ol (12).[34] To a stirred solution of 3-bromofuran (0.90 mL, 10.0 mmol, 200 mol%) in THF (10 mL) at –78 °C was added *t*-BuLi (12.4 mL, 20.0 mmol, 400 mol%) dropwise. After 15 min, 2-methyl propenal (0.41 mL, 5.0 mmol, 100 mol%) was added dropwise. After 1 h 15 min, sat. aq. NH_4Cl (5 mL) was added and the biphasic solution

was allowed to warm to rt. The phases were separated, the aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Crude alcohol **12** (0.90 g) was used without further purification for the next reaction. TLC (25% EtOAc in hexanes): R_f = 0.3; ^{1}H NMR: □ 7.42-7.40 (m, 1H), 7.38 (br t, *J* = 1.7 Hz, 1H), 6.34 (br dd, *J* = 0.6, 1.7 Hz, 1H), 5.17-5.14 (m, 1H), 5.12 (br s, 1H), 4.96-4.93 (m, 1H), 1.70 (s, 3H).

5-(*tert*-Butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentan-1-ol (13). To a stirred solution of *tert*-butyldimethylsilanyloxy-4-bromopent-4-ene[35] (0.21 g, 0.76 mmol, 100 mol%) in THF (4.0 mL) at –78 °C was added *t*-BuLi (1.35 mL, 1.9 mmol, 250 mol%) dropwise. After 20 min, 3-furaldehyde (50) (95 □L, 1.1 mmol, 150 mol%) was added. After 40 min, the solution was allowed to warm to rt and concentrated. The residue was dissolved in EtOAc (10 mL) and washed with sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 5-15% EtOAc in hexanes) provided furyl alcohol **13** as a colorless oil (0.137 g, 61%). TLC (20% EtOAc in hexanes): R_f = 0.3; ^{1}H NMR: □ = 7.42-7.39 (m, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 6.32 (br dd, *J* = 0.7, 1.7 Hz, 1H), 5.22 (br s, 1H), 5.15 (br d, *J* = 3.7 Hz, 1H), 4.97 (br d, *J* = 0.7 Hz, 1H), 3.62 (t, *J* = 6.2 Hz, 2H), 2.22 (d, *J* = 3.7 Hz, 1H), 2.16-1.96 (m, 2H), 1.77-1.62 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR: δ = 150.3, 143.2, 139.8, 127.4, 110.4, 109.0, 70.7, 62.7, 31.1, 28.0, 25.9, 18.3, –5.3; IR (film): ν_{max} = 3401, 1650, 1503 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{16}H_{28}O_3NaSi$ 319.1705 (M + Na^+); found: 319.1683.

General procedure A for preparation of malonates[19]

To a stirred solution of the alcohol (100 mol%), mono-ethyl malonate (**15a**)[36] or mono-*t*-butyl malonate (**15b**)[8,36,37] (110 mol%) and DMAP (10 mol%) in CH_2Cl_2 (0.5 M) at 0 °C was added DCC (120 mol%). After 1-2 h at rt, the mixture was filtered, washed twice with HCl (0.5 M) and sat. aq. $NaHCO_3$ and once with brine, dried, filtered and concentrated.

Ethyl-2-methyl-1-phenylallyl malonate (16). Prepared according to the general procedure A with alcohol **11** (1.00 g, 6.8 mmol, 100 mol%), mono-ethyl malonate **15a** (1.04 mL, 8.8 mmol, 130 mol%), DMAP (82 mg, 0.68 mmol, 10 mol%), CH_2Cl_2 (35 mL) and DCC (1.81 g, 8.8 mmol, 130 mol%). Flash column chromatography (silica, 2.5-10% EtOAc in hexanes) provided malonate **16** as a yellowish oil (1.12 g, 63%). TLC (20% EtOAc in hexanes): R_f = 0.38; ^{1}H NMR: δ = 7.36-7.27 (m, 5H), 6.22 (br s, 1H), 5.14 (br d, *J* = 0.8 Hz, 1H), 5.01 (br d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 2H), 1.65 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 166.3, 165.4, 142.5, 137.8, 128.4, 128.2, 127.0, 113.1, 79.5, 61.5, 41.9, 18.7, 14.0; IR (film): ν_{max} = 1752, 1736, 1654 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{15}H_{18}O_4Na$ 285.1103 (M + Na^+); found: 285.1118.

Ethyl-1-furan-3-yl-2-methylallyl malonate (17). Prepared according to the general procedure A with alcohol **12** (crude, 0.69 g, 5.0 mmol, 100 mol%), mono-ethyl malonate **15a** (0.77 mL, 6.5 mmol, 130 mol%), DMAP (61 mg, 0.50 mmol, 10 mol%), CH_2Cl_2 (25 mL) and DCC (1.34 g, 6.5 mmol, 130 mol%). Flash column chromatography (silica, 2.5-7.5 % EtOAc in hexanes)

provided the malonate **17** as a colorless oil (0.84 g, 67%). TLC (20% EtOAc in hexanes): R_f = 0.4; ^{1}H NMR: δ = 7.44-7.41 (m, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 6.33 (br dd, *J* = 0.6, 1.7 Hz, 1H), 6.20 (br s, 1H), 5.13 (br d, *J* = 0.8 Hz, 1H), 5.00 (br d, *J* = 0.8 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.41 (s, 2H), 1.72 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: δ = 166.3, 165.4, 143.3, 141.8, 140.8, 123.0, 113.2, 109.3, 72.7, 61.6, 41.8, 18.7, 14.0; IR (film): ν_{max} = 1734, 1655 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{13}H_{16}O_5Na$ 275.0895 (M + Na$^+$); found: 275.0901.

Ethyl-5-(*tert*-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl malonate (18). Prepared according to the general procedure A with alcohol **13** (58 mg, 0.20 mmol, 100 mol%), mono-ethyl malonate **15a** (25 μL, 0.22 mmol, 110 mol%), DMAP (2.4 mg, 20 μmol, 10 mol%), CH_2Cl_2 (0.4 mL) and DCC (61 mg, 0.30 mmol, 150 mol%). Flash column chromatography (silica, 2.5-7.5% EtOAc in hexanes) provided malonate **18** as a yellowish oil (65 mg, 81%). TLC (20% EtOAc in hexanes): R_f = 0.48; ^{1}H NMR: δ = 7.44-7.40 (m, 1H), 7.36 (br t, *J* = 1.7 Hz, 1H), 6.33 (br s, 1H), 6.22 (br s, 1H), 5.20 (s, 1H), 5.02 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 3.39 (s, 2H), 2.14-1.98 (m, 2H), 1.71-1.62 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR: δ = 166.3, 165.4, 145.9, 143.3, 141.1, 123.2, 111.7, 109.5, 72.0, 62.5, 61.5, 41.8, 30.8, 28.5, 25.9, 18.3, 14.0, –5.3; IR (film): ν_{max} 1752, 1735, 1650, 1503 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{21}H_{34}O_6NaSi$ 433.2022 (M + Na$^+$); found: 433.2036.

***tert*-Butyl-5-(*tert*-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl malonate (19).** Prepared according to the general procedure A with alcohol **13** (71 mg, 0.24 mmol, 100 mol%), mono-*t*-butyl malonate **15b** (26 μL, 0.29 mmol, 120 mol%), DMAP (2.9 mg, 24 μmol, 10 mol%), CH_2Cl_2 (0.5 mL) and DCC (74 mg, 0.36 mmol, 150 mol%). Flash column chromatography (silica, 2.5-10% EtOAc in hexanes) provided malonate **19** as a yellowish oil (92 mg, 88%). TLC (20% EtOAc in hexanes): R_f = 0.6; ^{1}H NMR: δ = 7.42 (br s, 1H), 7.36 (br t, *J* = 1.7 Hz, 1H), 6.33 (br s, 1H), 6.21 (br s, 1H), 5.21 (s, 1H), 5.02 (s, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.31 (s, 2H), 2.12-1.98 (m, 2H), 1.69-1.61 (m, 2H), 1.43 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR: δ = 165.8, 165.4, 145.9, 143.2, 141.1, 123.3, 111.5, 109.5, 82.1, 71.7, 62.5, 43.2, 30.8, 28.5, 27.9, 25.9, 18.3, –5.3; IR (film): ν_{max} = 1749, 1732, 1651, 1503 cm^{-1}; HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{38}O_6NaSi$ 461.2335 (M + Na$^+$); found: 461.2360.

Ethyl-5-(*tert*-butyldiphenylsilanyloxy)-(1*S*)-furan-3-yl-2-methylenepentyl malonate (20). Prepared according to the general procedure A with alcohol (*S*)-**14** (0.86 g, 2.1 mmol, 100 mol%), mono-ethyl malonate **15a** (0.24 mL, 2.1 mmol, 100 mol%), DMAP (25 mg, 0.21 mmol, 10 mol%), CH_2Cl_2 (4.1 mL) and DCC (0.55 g, 2.7 mmol, 130 mol%). Dry-column flash chromatography[38] (silica, 0-20% EtOAc in hexanes) provided malonate **20** as a yellowish oil (1.06 g, 97%). TLC (20% EtOAc in hexanes): R_f = 0.43; $[\alpha]_{20}^D$ –7.9 (*c* 1.0, $CHCl_3$; 59% ee); ^{1}H NMR: δ = 7.68-7.62 (m, 4H), 7.45-7.35 (m, 8H), 6.33 (br dd, *J* = 1.8, 0.6 Hz, 1H), 6.22 (br s, 1H), 5.21 (br s, 1H), 5.00 (br s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.40 (s, 2H), 2.20-2.03 (m, 2H), 1.77-1.65 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR: δ = 166.3, 165.4, 145.8, 143.3, 141.0, 135.5, 133.9, 129.5, 127.6, 123.1, 111.6, 109.4, 71.9, 63.2, 61.5, 41.8, 30.5, 28.4, 26.8, 19.2, 14.0; IR (film): ν_{max} = 1735 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{31}H_{38}O_6NaSi$ 557.2335 (M + Na$^+$); found: 557.2337.

***tert*-Butyl-5-(*tert*-butyldiphenylsilanyloxy)-(1*S*)-furan-3-yl-2-methylenepentyl malonate (21).** Prepared according to the general procedure A with alcohol (*S*)-**14** (0.87 g, 2.1 mmol, 100 mol%), mono-*t*-butyl malonate **15b** (0.33 g, 2.1 mmol, 100 mol%), DMAP (25 mg, 0.21 mmol, 10 mol%), DCC (0.51 g, 2.5 mmol, 120 mol%) and CH_2Cl_2 (4.2 mL). The reaction provided malonate **21** as a yellow oil (1.14 g, 98%), which was sufficiently pure to be used in the next step. An analytical sample was purified by dry-column flash chromatography[39] (silica, 0-15% EtOAc in hexanes). TLC (20% EtOAc in hexanes): R_f = 0.40; $[\alpha]_{20}^{D}$ –19 (c 1.0, CHCl3); ^{1}H NMR: δ = 7.68-7.61 (m, 4H), 7.45-7.34 (m, 8H), 6.32 (br dd, J = 1.7, 0.6 Hz, 1H), 6.21 (br s, 1H), 5.21 (br s, 1H), 4.99 (br s, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.30 (s, 2H), 2.18-2.02 (m, 2H), 1.76-1.64 (m, 2H), 1.43 (s, 9H), 1.02 (s, 9H); ^{13}C NMR: δ = 165.7, 165.4, 145.8, 143.2, 141.0, 135.5, 133.9, 129.5, 127.6, 123.2, 111.5, 109.4, 82.0, 71.6, 63.2, 43.1, 30.5, 28.5, 27.8, 26.8, 19.1; IR (film): ν_{max} = 1728, 1649, 1588 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{33}H_{42}O_5NaSi$ 585.2648 (M + Na$^+$); found: 585.2625.

General procedure B for preparation of diazomalonates[21]

To a stirred solution of the malonate (100 mol%) in MeCN (0.5 M) was added powdered and dried K_2CO_3 (105 mol%) followed by TsN_3 (105 mol%)[20] in MeCN. After 2 h, the solvent was evaporated. The residue was dissolved in Et_2O and the resulting solution washed twice with K_2CO_3 (10% aq. soln.), dried, filtered and concentrated. The residue was dissolved in Et_2O and hexanes were added to precipitate $TsNH_2$. The mixture was filtered through a pad of silica (10% Et_2O in hexanes flush) and concentrated. Generally the products were used without further purification for the cyclopropanation reaction.

Ethyl-2-methyl-1-phenylallyl diazomalonate (22). Prepared according to the general procedure B with malonate **16** (1.00 g, 3.8 mmol, 100 mol%), MeCN (7.6 mL), TsN_3 (0.79 g, 4.0 mmol, 105 mol%) and K_2CO_3 (0.55 g, 4.0 mmol, 105 mol%). The reaction provided diazomalonate **22** as a yellow oil (1.2 g), which was sufficiently pure for the next reaction. TLC (20% EtOAc in hexanes): R_f = 0.38; ^{1}H NMR: δ = 7.40-7.26 (m, 5H), 6.31 (br s, 1H), 5.19 (br d, *J* = 0.8 Hz, 1H), 5.01 (br d, *J* = 0.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.65 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 160.8, 160.2, 142.5, 137.9, 128.4, 128.1, 126.9, 113.0, 79.5, 61.6, 18.5, 14.3; IR (film): ν_{max} = 2142, 1761, 1735, 1693, 1653 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{15}H_{16}N_2O_4Na$ 311.1008 (M + Na$^+$); found: 311.1003.

Ethyl-1-furan-3-yl-2-methylallyl diazomalonate (23). Prepared according to the general procedure B with malonate **17** (0.82 g, 3.2 mmol, 100 mol%), MeCN (6.5 mL), TsN_3 (0.67 g, 3.4 mmol, 105 mol%) and K_2CO_3 (0.47 g, 3.4 mmol, 105 mol%). The reaction provided diazomalonate **23** as a yellow oil (0.64 g, 71%). TLC (20% EtOAc in hexanes): R_f = 0.4; ^{1}H NMR: δ = 7.46-7.44 (m, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 6.35 (br dd, *J* = 1.7, 0.7 Hz, 1H), 6.28 (br s, 1H), 5.16 (br d, *J* = 0.8 Hz, 1H), 5.01 (br d, *J* = 0.8 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.72 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 160.8, 160.3, 143.3, 141.9, 141.0, 123.1, 113.1, 109.2, 72.6, 61.7, 18.6, 14.3; IR (film): ν_{max} = 2142, 1759, 1732, 1690, 1655, 1504 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{13}H_{14}N_2O_5Na$ 301.0800 (M + Na$^+$); found: 301.0817.

Ethyl-5-(*tert*-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl diazomalonate (24). Prepared according to the general procedure B with malonate **18** (60 mg, 0.15 mmol, 100 mol%), MeCN (0.3 mL), TsN_3 (30 mg, 0.15 mmol, 105 mol%) and K_2CO_3 (21 mg, 0.15 mmol, 105 mol%). The reaction provided diazomalonate **24** as a yellow oil (59 mg, 92%). TLC (20% EtOAc in hexanes): R_f = 0.48; ^{1}H NMR: δ = 7.46-7.43 (m, 1H), 7.37 (br t, J = 1.6 Hz, 1H), 6.36-6.34 (m, 1H), 6.30 (br s, 1H), 5.24 (s, 1H), 5.03 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.58 (t, J = 6.3 Hz, 2H), 2.15-1.98 (m, 2H), 1.70-1.61 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR: δ = 160.8, 160.2, 145.9, 143.3, 141.2, 123.2, 111.6, 109.4, 71.9, 62.4, 61.7, 30.8, 28.5, 25.9, 18.2, 14.3, –5.4; IR (film): ν_{max} = 2141, 1762, 1735, 1693, 1651, 1503 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{21}H_{32}N_2O_6NaSi$ 459.1927 (M + Na$^+$); found: 459.1930.

***tert*-Butyl-5-(*tert*-butyldimethylsilanyloxy)-1-furan-3-yl-2-methylenepentyl diazomalonate (25).** Prepared according to the general procedure B with malonate **19** (80 mg, 0.18 mmol, 100 mol%), MeCN (0.4 mL), TsN_3 (38 mg, 0.19 mmol, 105 mol%) and K_2CO_3 (27 mg, 0.19 mmol, 105 mol%). The reaction provided diazomalonate 25 as a yellow oil (79 mg, 93%). TLC (20% EtOAc in hexanes): R_f = 0.6; ^{1}H NMR: δ = 7.45-7.42 (m, 1H), 7.36 (br t, *J* = 1.6 Hz, 1H), 6.36-6.33 (m, 1H), 6.31 (br s, 1H), 5.22 (s, 1H), 5.03 (s, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.14-1.98 (m, 2H), 1.70-1.60 (m, 2H), 1.51 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR: δ = 160.4, 159.7, 146.0, 143.3, 141.2, 123.3, 111.6, 109.4, 83.1, 71.5, 62.4, 30.8, 28.5, 28.2, 25.9, 18.3, –5.4; IR (film): ν_{max} = 2137, 1759, 1731, 1688, 1503 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for C23H36N2O6NaSi 487.2224 (M + Na$^+$); found: 487.2240.

Ethyl-5-(*tert*-butyldiphenylsilanyloxy)-(1*S*)-furan-3-yl-2-methylenepentyl diazomalonate (26). Prepared according to the general procedure B with malonate **20** (1.06 g, 2.0 mmol, 100 mol%), MeCN (4.0 mL), TsN_3 (0.41 g, 2.1 mmol, 105 mol%) and K_2CO_3 (0.29 g, 2.1 mmol, 105 mol%). Reaction provided diazomalonate **26** as a yellow oil (1.10 g, quant.). TLC (20% EtOAc in hexanes): R_f = 0.43; $[\alpha]_{20}^D$ –15.9 (c 1.0, CHCl3; 59% ee); ^{1}H NMR: δ = 7.67-7.61 (m, 4H), 7.45-7.33 (m, 8H), 6.34 (br dd, J = 1.8, 0.6 Hz, 1H), 6.30 (br s, 1H), 5.23 (br s, 1H), 5.01 (br s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.64 (t, J = 6.2 Hz, 2H), 2.19-2.04 (m, 2H), 1.76-1.65 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR: δ = 160.8, 160.2, 145.8, 143.3, 141.2, 135.5, 133.9, 129.5, 127.6, 123.1, 111.7, 109.3, 71.8, 63.2, 61.7, 30.5, 28.5, 26.8 19.2, 14.3; IR (film): ν_{max} = 2141, 1759, 1734, 1691, 1589, 1503 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{31}H_{36}N_2O_6NaSi$ 583.2240 (M + Na$^+$); found:583.2226.

***tert*-Butyl-5-(*tert*-butyldiphenylsilanyloxy)-(1*S*)-furan-3-yl-2-methylenepentyl diazomalonate (27).** Prepared according to the general procedure B with malonate **21** (2.06 g, 3.7 mmol, 100 mol%), MeCN (7.7 mL), K_2CO_3 (0.56 g, 4.1 mmol, 110 mol%) and TsN_3 (0.80 g, 4.1 mmol, 100 mol%). Dry column flash chromatography2 (silica, 5-15% EtOAc in hexanes) provided diazomalonate **27** as a yellow oil (2.11 g, 98%). TLC (20% EtOAc in hexanes): R_f = 0.4; $[\alpha]_{20}^D$ –22 (c 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.68-7.61 (m, 4H), 7.45-7.33 (m, 8H), 6.33 (br dd, J = 1.8, 0.7 Hz, 1H), 6.30 (br s, 1H), 5.20 (br s, 1H), 4.99 (br s, 1H), 3.64 (t, J = 6.2 Hz, 2H), 2.18-2.02 (m, 2H), 1.74-1.64 (m, 2H), 1.51 (s, 9H), 1.02 (s, 9H); ^{13}C NMR: δ = 168.6, 159.6, 145.9, 143.2, 141.2, 135.5, 133.9, 129.5, 127.6, 123.2, 111.6, 109.4, 83.1, 71.4, 63.2, 30.6, 28.5,

28.2, 26.8, 19.1; IR (film): ν_{max} = 2137, 1755, 1729, 1686, 1588 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{33}H_{40}N_2O_6NaSi$ 611.2553 ($M + Na^+$); found: 611.2548.

(5*S*)-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-(4*S*)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1*S*)-carboxylic acid tert-butyl ester (28a) and (5*R*)-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-(4*S*)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1*R*)-carboxylic acid tert-butyl ester (28b)To a stirred solution of diazomalonate **27** (1.15 g, 2.0 mmol, 100 mol%) in DCE (17 mL) was added the catalytic complex **10a** (38 mg, 59 μmol, 3 mol%). The solution was heated up to 55 °C, the temperature at which the mixture started to effervesce and turned brown in color. After 24 h, all diazocompound had been consumed as judged by TLC, the solution was cooled to rt and concentrated. The residue was dissolved in MTBE, stirred with activated carbon for 5 min, filtered through a pad of Celite® and concentrated. Flash column chromatography (silica, 5-15% EtOAc in hexanes) provided cyclopropanolactones **28a** and **28b** (184 and 149 mg, respectively, 30% in total) as a greenish-yellow oil.

28[a]. TLC (20% EtOAc in hexanes): R_f = 0.36; $[\alpha]_{20}^D$ +4.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.62-7.55 (m, 4H), 7.46-7.34 (m, 8H), 6.41 (br s, 1H), 5.24 (s, 1H), 3.61-3.49 (m, 2H), 1.83 (d, *J* = 4.9 Hz, 1H), 1.79-1.67 (m, 1H), 1.66-1.54 (m, 2H), 1.53 (s, 9H), 1.38 (d, *J* = 4.9 Hz, 1H), 1.35-1.24 (m, 1H), 1.00 (s, 9H); ^{13}C NMR: δ = 171.3, 164.5, 144.3, 141.2, 135.5, 133.6, 129.7, 127.6, 122.0, 107.9, 82.9, 75.8, 63.0, 40.8, 36.4, 29.9, 28.1, 26.7, 24.1, 22.6, 19.1; IR (film): ν_{max} = 1784, 1727, 1506 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{33}H_{40}O_6NaSi$ 583.2492 ($M + Na^+$); found: 583.2474.

28b. TLC (20% EtOAc in hexanes): R_f = 0.43; $[\alpha]_{20}^D$ –27 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.70-7.60 (m, 4H), 7.47-7.32 (m, 8H), 6.38 (br s, 1H), 5.41 (s, 1H), 3.72-3.55 (m, 2H), 2.06 (dd, *J* = 11.7, 10.4 Hz, 1H), 1.86 (d, *J* = 4.9 Hz, 1H), 1.77-1.67 (m, 2H), 1.55-1.45 (m, 2H), 1.49 (s, 9H), 1.04 (s, 9H); ^{13}C NMR: δ = 170.7, 164.6, 143.9, 140.4, 135.5, 133.6, 129.7, 127.7, 120.9, 108.6, 82.9, 74.5, 63.2, 42.5, 36.0, 29.5, 28.0, 26.8, 25.0, 22.8, 19.2; IR (film): ν_{max} = 1787, 1721, 1500 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for C33H40O6NaSi 583.2493 ($M + Na^+$); found: 583.2482.

(4*S*)-Furan-3-yl-(5*S*)-(3-hydroxypropyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-(1*S*)-carboxylic acid tert-butyl ester (29a). To a stirred solution of cyclopropanolactone **28a** (0.38 g, 0.67 mmol, 100 mol%) in THF (1.4 mL) at 0 °C was added TBAF (1 M in THF, 1.34 mL, 1.3 mmol, 200 mol%) dropwise. After 30 min at 0 °C, the brown solution was allowed to warm to rt and after 2 h, sat. aq. NH_4Cl (2 mL) was added. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 0-2% MeOH in CH_2Cl_2 with 2% Et_3N) provided alcohol **29a** as a brown oil (0.123 g, 57 %). TLC (50% EtOAc in hexanes): R_f = 0.18; $[\alpha]_{20}^D$ +53 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.55-7.51 (m, 1H), 7.47 (br t, *J* = 1.7 Hz, 1H), 6.42 (br dd, *J* = 1.7, 0.7 Hz, 1H), 5.33 (s, 1H), 3.55 (br t, *J* = 5.9 Hz, 2H), 1.87 (d, *J* = 4.9 Hz, 1H), 1.72-1.55 (m, 3H), 1.53 (s, 9H), 1.43 (dd, *J* = 4.9, 1.5 Hz, 1H), 1.35-1.28 (m, 1H); ^{13}C NMR: δ = 171.2, 164.5, 144.4, 141.3, 122.0, 107.9, 83.1, 75.8, 62.0, 40.9, 36.3, 29.9, 28.1, 23.8, 22.8; IR

(film): ν_{max} = 3523, 1778, 1725, 1507 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{17}H_{22}O_6Na$ 345.1314 ($M + Na^+$); found: 345.1302.

(4*S*)-Furan-3-yl-(5*R*)-(3-hydroxypropyl)-2-oxo-3-oxabicyclo[3.1.0]hexane-(1*R*)-carboxylic acid tert-butyl ester (29b): Prepared from **28a** as described for **29a**. Reaction time 3 h. 80% yield. TLC (50% EtOAc in hexanes): R_f = 0.22; $[\alpha]_{20}^D$ –74 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.50-7.48 (m, 1H), 7.44 (t, *J* = 1.8 Hz, 1H), 6.41 (br dd, *J* = 1.8, 0.7 Hz, 1H), 5.48 (s, 1H), 3.70-3.57 (m, 2H), 2.04 (td, *J* = 11.2, 1.2 Hz, 1H), 1.88 (d, *J* = 5.1 Hz, 1H), 1.82-1.54 (m, 3H), 1.52 (s, 9H), 1.53-1.51 (m, 1H); ^{13}C NMR: δ = 170.6, 164.7, 144.0, 140.5, 120.8, 108.7, 83.1, 74.4, 62.1, 42.4, 36.0, 29.4, 28.0, 24.8, 23.0; IR (film): ν_{max} = 3413, 1781, 1719, 1505 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{17}H_{22}O_6Na$ 345.1314 ($M + Na^+$); found: 345.1306.

(4*S*)-Furan-3-yl-2-oxo-(5*S*)-(3-phenylsulfanylpropyl)-3-oxabicyclo[3.1.0]hexane-(1*S*)-carboxylic acid tert-butyl ester (30a). A stirred solution of alcohol **29a** (0.12 g, 0.38 mmol, 100 mol%) and $(SPh)_2$ (0.13 g, 0.45 mmol, 120 mol%) in pyridine (1.9 mL) at 0 °C was bubbled with argon for 10 min after which freshly distilled Bu_3P (0.19 mL, 0.76 mmol, 200 mol%) was added. After 15 min at 0 °C, the solution was allowed to warm to rt. After 1.5 h, Et_2O (10 mL) was added and the solution was washed with sat. aq. $NaHCO_3$ (5 mL) and brine, dried, filtered and concentrated. Flash column chromatography (silica, 10-15 % EtOAc in hexanes) provided sulfide **30a** as a colorless oil (0.118 g, 75%). TLC (50% EtOAc in hexanes): R_f = 0.65; $[\alpha]_{20}^D$ +41 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.47 (br t, *J* = 1.6 Hz, 1H), 7.36 (s, 1H), 7.33-7.17 (m, 5H), 6.39-6.35 (m, 1H), 5.23 (s, 1H), 2.88-2.71 (m, 2H), 1.84 (d, *J* = 5.0 Hz, 1H), 1.76-1.60 (m, 3H), 1.53 (s, 9H), 1.40 (dd, *J* = 5.0, 1.2 Hz, 1H), 1.37-1.23 (m, 1H); ^{13}C NMR: δ = 171.0, 164.4, 144.4, 141.2, 135.7, 129.4, 128.9, 126.2, 121.8, 107.7, 83.1, 75.6, 40.7, 36.1, 33.2, 28.1, 26.54, 26.48, 22.7; IR (film): ν_{max} = 1783, 1725, 1584, 1506 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{26}O_5NaS$ 437.1399 ($M + Na^+$); found: 437.1396.

(4*S*)-Furan-3-yl-2-oxo-(5*R*)-(3-phenylsulfanylpropyl)-3-oxabicyclo[3.1.0]hexane-(1*R*)-carboxylic acid tert-butyl ester (30b). Prepared from **29a** as described for **30a**. Reaction time 2.5 h. 65% yield. TLC (50% EtOAc in hexanes): R_f = 0.70; $[\alpha]_{20}^D$ –49 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.43 (br t, *J* = 1.7 Hz, 1H), 7.42-7.40 (m, 1H), 7.33-7.25 (m, 4H), 7.23-7.16 (m, 1H), 6.35 (br dd, *J* = 1.7, 0.8 Hz, 1H), 5.36 (s, 1H), 2.96-2.78 (m, 2H), 2.07 (td, *J* = 11.9, 1.8 Hz, 1H), 1.86 (d, *J* = 5.1 Hz, 1H), 1.83-1.73 (m, 2H), 1.70-1.60 (m, 1H), 1.49 (s, 9H), 1.51-1.45 (m, 1H); ^{13}C NMR: δ = 170.3, 164.5, 143.9, 140.5, 135.6, 129.7, 129.0, 126.4, 108.6, 99.8, 83.1, 74.3, 42.1, 36.0, 33.7, 28.0, 27.4, 26.0, 22.7; IR (film): ν_{max} = 1785, 1719, 1584, 1504 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{26}O_5NaS$ 437.1399 ($M + Na^+$); found: 437.1388.

(5*S*)-(3-Benzenesulfonylpropyl)-(4*S*)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1*S*)-carboxylic acid tert-butyl ester (31a). To a stirred solution of sulfide **30a** (82 mg, 0.20 mmol, 100 mol%) in CH_2Cl_2 (1.0 mL) at 0 °C was added $NaHCO_3$ (0.17 g, 2.0 mmol, 1000 mol%) and *m*-CPBA (70%, 0.11 g, 0.46 mmol, 230 mol%). After 60 min, sat. aq. $NaHCO_3$ (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 33-50% EtOAc in hexanes) provided sulfone **31a** as a white foam (77 mg, 88%). TLC (50% EtOAc

in hexanes): R_f = 0.43; $[\alpha]_{20}^{D}$ +29 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.87-7.81 (m, 2H), 7.71-7.69 (m, 1H), 7.61-7.54 (m, 2H), 7.45 (br t, *J* = 1.6 Hz, 1H), 7.39 (br s, 1H), 6.33 (br dd, *J* = 1.6, 0.7 Hz, 1H), 5.25 (s, 1H), 3.07-2.85 (m, 2H), 1.81 (d, *J* = 5.1 Hz, 1H), 1.83-1.62 (m, 3H), 1.49 (s, 9H), 1.42 (dd, *J* = 5.1, 1.3 Hz, 1H), 1.31-1.21 (m, 1H); ^{13}C NMR: δ = 170.6, 164.2, 144.6, 141.2, 138.9, 133.9, 129.4, 127.9, 121.6, 107.6, 83.4, 75.3, 55.5, 40.3, 35.9, 28.1, 26.2, 22.6, 20.3; IR (film): ν_{max} = 1781, 1724, 1586, 1506 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{26}O_7NaS$ 469.1297 (M + Na^+); found: 469.1289.

(5*R*)-(3-Benzenesulfonylpropyl)-(4*S*)-furan-3-yl-2-oxo-3-oxabicyclo[3.1.0]hexane-(1*R*)-carboxylic acid tert-butyl ester (31b). Prepared from **30a** as described for **31a**. Reaction time 2 h. 80% yield. TLC (50% EtOAc in hexanes): R_f = 0.53; $[\alpha]_{20}^{D}$ –54 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ = 7.89-7.83 (m, 2H), 7.70-7.64 (m, 1H), 7.62-7.53 (m, 2H), 7.48-7.42 (m, 2H), 6.41-6.37 (m, 1H), 5.40 (s, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 2.09-1.90 (m, 2H), 1.83 (d, *J* = 5.2 Hz, 1H), 1.85-1.63 (m, 2H), 1.52 (d, *J* = 5.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR: δ = 170.0, 164.5, 144.1, 140.7, 138.9, 133.9, 129.4, 127.9, 120.5, 108.6, 83.4, 74.1, 55.7, 41.7, 35.8, 27.9, 27.1, 22.7, 20.0; IR (film): ν_{max} = 1784, 1718, 1586, 1505 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{26}O_7NaS$ 469.1297 (M + Na^+); found: 469.1311.

Ketosulfone 32a. To a stirred solution of sulfone **31a** (77 mg, 0.17 mmol, 100 mol%) in THF (3.5 mL, freshly distilled from $LiAlH_4$) at –100 °C was added n-BuLi (0.16 mL, 0.35 mmol, 200 mol%) dropwise. After 15 min, more n-BuLi (15 μL, 34 μmol, 20 mol%) was added because some starting material was evident by TLC analysis. After 25 min, sat. aq. NH_4Cl was added and the mixture was allowed to warm to rt. The aqueous phase was extracted with EtOAc and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 40-60% EtOAc in hex) provided ketosulfone **32a** as mixture of diastereomers (**a**:**b** = 1:0.8, 33 mg, 55%). TLC (50% EtOAc in hexanes): R_f = 0.1; ^{1}H NMR: δ = 7.87-7.83 (m, 2H, b), 7.82-7.77 (m, 2H, a), 7.72-7.66 (m, 2H, a+b), 7.60-7.54 (m, 5H, 3a+2b), 7.48 (br t, *J* = 1.7 Hz, 1H, a), 7.46-7.43 (m, 2H, b), 6.73 (br dd, *J* = 1.7, 0.7 Hz, 1H, a), 6.20 (br t, *J* = 1.4 Hz, 1H, b), 5.47 (s, 1H, a), 5.45 (s, 1H, b), 3.76 (dd, *J* = 10.0, 8.7 Hz, 1H, b), 3.59 (dd, *J* = 5.6, 1.9 Hz, 1H, a), 2.88-2.80 (m, 1H, a), 2.86 (d, *J* = 6.4 Hz, 1H, b), 2.48-2.30 (m, 3H, a+2b), 2.20 (dt, *J* = 14.2, 4.1 Hz, 1H, b), 2.02-1.89 (m, 2H, a), 1.92 (d, *J* = 5.9 Hz, 1H, a), 1.81-1.71 (m, 1H, b), 1.81 (d, *J* = 6.4 Hz, 1H, b), 1.70 (d, *J* = 5.9 Hz, 1H, a); ^{13}C NMR: δ = 189.7 (a), 189.2 (b), 168.0 (a/b), 167.9 (a/b), 144.7 (b), 144.2 (a), 141.7 (a), 140.6 (b), 138.2 (a), 137.6 (b), 134.39 (a), 134.35 (b), 129.23 (a/b), 129.17 (2a/b), 129.1 (a/b), 121.5 (b), 120.7 (a), 109.2 (a), 107.8 (b), 77.2 (a), 75.7 (b), 68.5 (b), 67.2 (a), 40.3 (b), 35.6 (b), 35.0 (a), 34.8 (a), 23.6 (b), 23.2 (a), 20.0 (b), 19.9 (b), 19.3 (a), 18.3 (a); IR (film): ν_{max} = 1780, 1704, 1583, 1503 cm^{-1}; HRMS (ESI+) *m*/*z* calcd. for $C_{19}H_{16}O_6NaS$ 395.0565 (M + Na^+); found: 395.0572.

Methyl ketone 33. To a stirred solution of ketosulfone **32a** (7.0 mg, 19 μmol, 100 mol%) in THF:H_2O (9:1, 1.0 mL) at 0 °C was added commercial aluminum foil (1.5 mg, 57 μmol, 300 mol%), which had been immersed in $HgCl_2$ (aq., 2%), washed with EtOH and Et_2O and cut into small pieces. After 1 h, more Al-foil (1.5 mg, 57 μmol, 300 mol%) was added and after 4 h, the mixture was filtered through a pad of Celite®, dried, filtered and concentrated. Flash column

chromatography (silica, 33-50% EtOAc in hex) provided methyl ketone **33** (2 mg, 45%). TLC (50% EtOAc in hexanes): R_f = 0.5; $[\alpha]_{20}^{D}$ –33 (*c* 0.23, $CHCl_3$; 46% ee); ^{1}H NMR: δ = 7.51 (s, 1H), 7.48 (s, 1H), 6.40 (s, 1H), 5.08 (s, 1H), 3.30 (br s, 1H), 2.48-2.33 (m, 2H), 2.06-1.97 (m, 1H), 1.78-1.66 (m, 2H), 1.33-1.20 (m, 1H), 1.29 (s, 3H); ^{13}C NMR: δ = 202.7, 170.8, 143.8, 140.2, 118.3, 108.6, 82.9, 63.1, 49.6, 39.6, 28.3, 21.3, 20.6; IR (film): ν_{max} = 1776, 1716, 1504 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{13}H_{14}O_4Na$ 257.0790 (M + Na^+); found: 257.0779.

Ketosulfone 32b. To a solution of sulfone **31b** (0.122 g, 0.273 mmol, 100 mol%) in THF (2.7 mL, freshly distilled from $LiAlH_4$) at –100 °C was added KHMDS (1 M in toluene, 1.4 mL, 0.68 mmol, 250 mol%) dropwise over 5 min. After 1.5 h, sat. aq. NH_4Cl was added and the mixture was allowed to warm to rt. The aqueous phase was extracted with EtOAc and the organic extracts were washed with brine, dried, filtered and concentrated. Flash column chromatography (silica, 33-50% EtOAc in hex) provided sulfone **31b** (28 mg) and ketosulfone **32b** as mixture of diastereomers (**a**:**b** = 1:0.4, 28 mg, 36% based on recovered **31b**). TLC (50% EtOAc in hexanes): R_f = 0.2; ^{1}H NMR: δ = 7.89-7.84 (m, 2H, b), 7.80-7.75 (m, 2H, a), 7.73-7.64 (m, 2H, a+b), 7.62-7.53 (m, 4H, 2a+2b), 7.53-7.50 (m, 1H, a), 7.50-7.46 (m, 3H, a+2b), 6.44-6.41 (m, 1H, a), 6.40-6-38 (m, 1H, b), 5.59 (s, 1H, a), 5.30 (s, 1H, b), 3.93 (dd, *J* = 10.4, 7.4 Hz, 1H, b), 3.60 (dd, *J* = 5.0, 2.1 Hz, 1H, a), 2.93 (ddt, *J* = 15.6, 5.6, 2.1 Hz, 1H, a), 2.74 (td, *J* = 13.9, 5.6 Hz, 1H, a), 2.66, (d, *J* = 6.5 Hz, 1H, b), 2.56-2.41 (m, 3H, b), 2.34 (ddd, *J* = 13.9, 5.0, 2.1 Hz, 1H, a), 2.24-2.12 (m, 1H, b), 1.97 (ddt, *J* = 15.6, 13.9, 5.0 Hz, 1H, a), 1.73 (d, *J* = 6.5 Hz, 1H, b), 1.67 (d, *J* = 6.2 Hz, 1H, a), 1.63 (d, *J* = 6.2 Hz, 1H, a); ^{13}C NMR: δ = 189.8 (a+b), 168.2 (a), 168.0 (b), 144.3 (b), 144.2 (a), 140.1 (b), 140.0 (a), 137.4 (a+b), 134.6 (a), 134.3 (b), 129.4 (a), 129.3 (b), 129.2 (b), 129.1 (a), 120.8 (a), 120.5 (b), 108.3 (a), 108.2 (b), 77.3 (a), 76.2 (b), 68.5 (b), 68.3 (a), 39.6 (b), 36.9 (b), 35.4 (a), 33.5 (a), 21.8 (b), 21.1 (b), 20.5 (a+b), 20.0 (a), 19.4 (a); IR (film): ν_{max} = 1784, 1708, 1635, 1503 cm^{-1}; HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{16}O_6NaS$ 395.0565 (M + Na^+); found: 395.0532.

Cyclopropyl ketone 34. To a stirred solution of ketosulfone **32b** (10.0 mg, 27 μmol, 100 mol%) in THF:H_2O (9:1, 1.4 mL) at 0 °C was added commercial aluminum foil (3.6 mg, 0.13 mmol, 500 mol%), which had been immersed in $HgCl_2$ (aq., 2%), washed with EtOH and Et_2O and cut into small pieces. After 30 min, the cooling bath was removed. After 2 h more Al-foil (3.6 mg, 0.13 mmol, 500 mol%) was added and after 3 h, the mixture was filtered through a pad of Celite®, dried, filtered and concentrated. Flash column chromatography (silica, 33-50% EtOAc in hex) provided cyclopropyl ketone **34** (2.5 mg, 40%). TLC (50% EtOAc in hexanes): R_f = 0.2; $[\alpha]_{20}^{D}$ –71 (*c* 0.2, $CHCl_3$); ^{1}H NMR: δ = 7.51-7.48 (m, 1H), 7.46 (t, *J* = 1.6 Hz, 1H), 6.42-6.40 (m, 1H), 5.40 (s, 1H), 2.42 (dt, *J* = 18, 4.6 Hz, 1H), 2.33 (dt, *J* = 13, 4.6 Hz, 1H), 2.24 (ddd, *J* = 18, 11, 6.2 Hz, 1H), 2.09 (ddd, *J* = 13, 11, 4.9 Hz, 1H), 2.03-1.92 (m, 1H), 1.94 (d, *J* = 6.0 Hz, 1H), 1.82-1.69 (m, 1H), 1.63 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR: δ = 197.6, 168.9, 144.2, 139.9, 121.0, 108.3, 76.9, 37.2, 36.8, 35.4, 23.9, 21.0, 19.3; IR (film): ν_{max} = 1785, 1695, 1505 cm^{-1}; HRMS (ESI+) *m*/*z* calcd. for $C_{13}H_{12}O_4Na$ 255.0633 (M + Na^+); found: 255.0640.

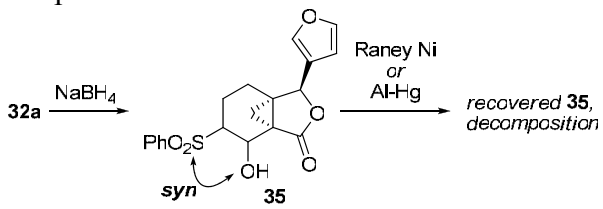
Acknowledgements

We thank Dr. Heikki Hassila for informative discussions regarding the cyclopropanation reactions as well as Ministry of Education in Finland, Finnish Cultural Foundation and Helsinki University of Technology for funding.

References and Notes

1. Mondon, A.; Epe, B. *Progr. Chem. Org. Nat. Prod.* **1983**, *44*, 101.
2. Pihko, A. J.; Koskinen, A. M. P. *Tetrahedron* **2005**, *61*, 8769.
3. Mondon, A.; Epe, B.; Callsen, H. *Liebigs Ann. Chem.* **1983**, 1760.
4. Mulholland, D. A.; McFarland, K.; Randrianarivelojosia, M.; Rabarison, H. *Phytochemistry* **2004**, *65*, 2929.
5. Mulholland, D.; Mahomed, H.; Kotsos, M.; Randrianarivelojosia, M.; Lavaucf, C.; Massiot, G.; Nuzillard, J.-M. *Tetrahedron* **1999**, *55*, 11547.
6. Pihko, A. J.; Lundell, K.; Kanerva, L.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2004**, *15*, 1637.
7. Koskinen, A. M. P.; Muñoz, L. *J. Chem. Soc., Chem. Commun.* **1990**, 1373.
8. Koskinen, A. M. P.; Muñoz, L. *J. Org. Chem.* **1993**, *58*, 879.
9. Koskinen, A. M. P.; Hassila, H. *J. Org. Chem.* **1993**, *58*, 4479.
10. (a) Koskinen, A. M. P.; Hassila, H. *Acta Chem. Scand.* **1996**, *50*, 323. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.
11. Hassila, H. Ph.D. Thesis, University of Oulu, 1998. *Transition metal catalysed intramolecular cyclopropanation*.
12. Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616.
13. Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2001**, 2151.
14. Rasmussen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O. *Chem. Eur. J.* **2002**, *8*, 177.
15. Evans, D. A.; Woerpel, K. A.; Hinman, M. H.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
16. Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90.
17. Doyle, M. P.; Peterson, C. S.; Zhou, G.-L.; Nishiyama, H. *Chem. Commun.* **1997**, 211.
18. Fryzuk, M. D.; Jafarpour, L.; Rettig, S. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3191.
19. Neises, B.; Steglich, W. *Org. Synth.* **1990**, *Coll. Vol. VII*, 92.
20. Koskinen, A. M. P.; Muñoz, L. *J. Chem. Soc. Chem. Comm.* **1990**, 652.
21. Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* **1973**, *Coll. Vol. V*, 179.

22. Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203.
23. Schinnerl, M.; Böhm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765.
24. Konosu, T.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2212.
25. Nagakawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.
26. Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994**, *59*, 4749.
27. Staley, S. W. Regioselectivity in the Reductive Cleavage of Cyclopropane Rings by Dissolving Metals. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience, 1972; Vol. 2, pp 309.
28. von Baeyer, A. *Chem. Ber.* **1895**, *28*, 1586.
29. Norin, T. *Acta Chem. Scand.* **1965**, *19*, 1289.
30. Dauben, W. G.; Deviny, E. J. *J. Am. Chem. Soc.* **1966**, *31*, 3794.
31. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
32. Jia, Y. X.; Li, X.; Wu, B.; Zhao, X. Z.; Tu, Y. Q. *Tetrahedron* **2002**, *58*, 1697.
33. Because the ketone functionality in **32a** was apparently activating the cyclopropyl ring too much, the ketone was reduced stereoselectively to provide a 1:1 mixture of α- and β-*syn*-hydroxysulfones **35** in 90% yield. However, reduction of the hydroxysulfones **35** with either Raney nickel or aluminum amalgam resulted in recovery of part of the starting material accompanied with decomposition.



34. Kelly, A. R.; Kerrigan, M. H.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 4097.
35. Paquette, L. A.; Hofferberth, J. E. *J. Org. Chem.* **2003**, *68*, 2266.
36. Breslow, D. S.; Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1286.
37. Gibson, F. S.; Park, M. S.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 7503.
38. Harwood, L. M. *Aldrichim. Acta* **1985**, *18*, 25.