Norbornanoid Chiral Ketones by Desymmetrization of Dibromoalkenes

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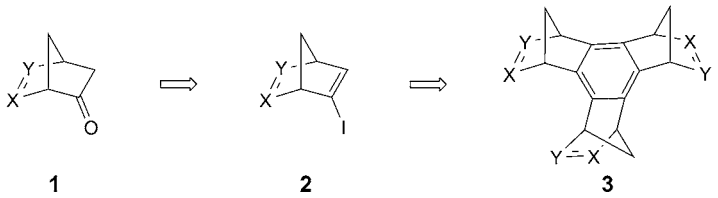
New optically active polycyclic ketones **6a**–**6d**, amenable to a large variety of synthetic applications, have been prepared from readily available 2,3-dibromonorbornene and analogs (*Scheme 2*) *via* desymmetrization with (−)-ephedrine, followed by hydrolysis under mild acidic conditions. At variance with substrates **4a**–**4d**, the sterically hindered norbornene derivative **4e** reacts with the solvent *N*-methylpyrrolidin-2-one (NMP) leading to the formation of the unusual cyclopropanoid products **8a** and **8b**.

Introduction. – The use of polycyclic ketones as intermediates in asymmetric synthesis is one of the cornerstones of organic chemistry since the first synthesis of prostaglandins developed at the end of 1960s [1]. During the last four decades, several molecules have been prepared by procedures entailing this sort of molecules, and the natural products dolabellatrienone [2] and (−)-sordarin [3] are some of the most recent reported examples. The polycyclic ketones are known for their biological activities, for example, as inhibitors of γ-secretase [4], cannabinoid receptor ligands [5], and calcium channel blockers [6]. Our interest regarding the enantiomerically pure norbornenone types **1** (bicyclo[2.2.1]hept-5-en-2-one) is due to their role in the synthesis of benzocyclotrimers [7] as outlined in *Scheme 1*. The transformation of the C=O moiety to the reactive iodo derivatives **2** by known procedures [7h][8] is the preferred way to produce selectively and in high yield enantiomerically pure *syn*-benzocyclotrimer **3**.

Scheme 1. *Enantiomerically Pure* syn-*Benzocyclotrimers* **3** *from Ketones* **1**



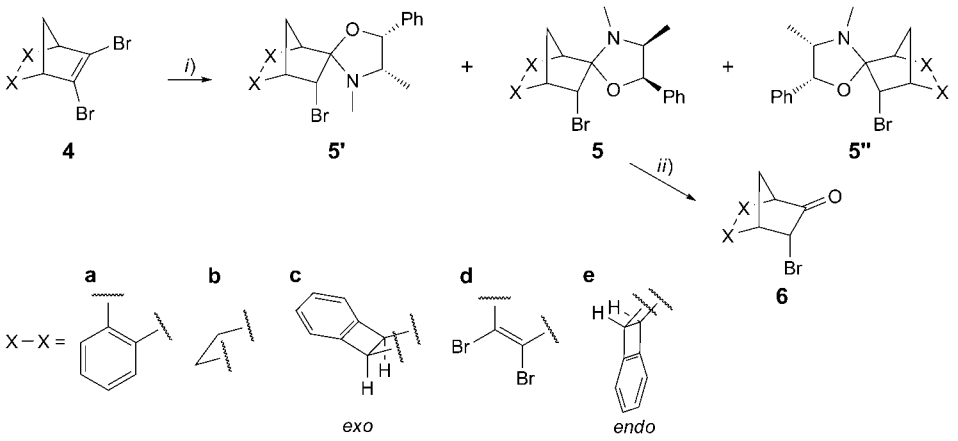
This type of compounds has recently been used as a platform to realize nanocapsules [7g], molecular cages [7a][7d], and receptors [7b], as well as a sumanene [9] and its derivatives [10].

Herein, we present a three-step synthesis of chiral norbornanoid ketones *via* a procedure that combines the versatility of high-temperature bromination [11] and the

desymmetrization of the formed 2,3-dibromonorbornenes with (−)-ephedrine [12]. Indeed, the high-temperature bromination allows an easy access to a variety of symmetrical dibromo olefins, which can be subjected to desymmetrization with (−)-ephedrine to give diastereoisomeric oxazolidines **5**, which are readily hydrolyzed to bromo ketones **6**. The use of dibromo olefins **4**, instead of the reported olefins bearing Cl or $PhSO_2$ groups [13] allows for simple operations [14], an advantageous atom economy with respect to the $PhSO_2$ groups [15], and, above all, a convenient access to a wide variety of norbornanoid substrates **4**, rendering this method of general utility in the field [16].

Results and Discussions. – As depicted in *Scheme 2*, five polycyclic dibromo olefins were submitted to desymmetrization with (−)-ephedrine to evaluate the effect of the steric hindrance of the reagents on the yields and selectivity.

Scheme 2



i) 1.5 equiv. of (−)-ephedrine, 3.0 equiv. of ^{t}BuOK, NMP, 16 h, 80°. *ii*) PPTS (Pyridinium *p*-toluenesulfonate), H_2O, THF, 2 d, r.t.

The results are collected in the *Table*. When substrate **4a** (*Entry 1*) was reacted with (−)-ephedrine under the reaction conditions that had turned out to be the best with analogous substrates [12] (^{t}BuOK as base, 1-methylpyrrolidin-2-one (NMP) as solvent at 80°), two out of the possible four diastereoisomers, **5a** and **5a′**, in a 90 : 10 ratio were obtained. This ratio was determined by integration of the *doublet*s at *ca.* δ(H) 5 in the ^{1}H-NMR spectrum attributed to the H-atoms H_{exo}–C(3) performed on the crude reaction mixture. The reaction is totally site-selective, *i.e.*, it occurs at the same prochiral C-atom, giving rise to two diastereoisomers with the same skeletal configuration, rendering this approach straightforward, because the hydrolysis of the crude reaction mixture gave a single enantiomer of ketone **6a** without any further resolution.

The configuration of **5a** shown in *Scheme 2* was determined by a thorough analysis of dipolar interactions in the NOESY spectra (available as *Supporting Information*).

Table. *Desymmetrization of Dibromo Compounds* **4**

Entry	Substrate	Product ratio **5**/**5′**/**5″**[a]) [%]	Yield of **5** [%]	de of **5**[a]) [%]	ee of **6**[b]) [%]
1	**4a**	90 : 10 : 0	82	> 99	≥ 99
2	**4b**	80 : 7 : 13	73	74	74
3	**4c**	80 : 9 : 11	73	78	97
4	**4d**	81 : 9 : 10	74	80	≥ 99
5	**4e**	–	–	–	–

[a]) Calculated on the basis of ^{1}H-NMR spectra. [b]) Calculated on the basis of HPLC analysis.

This study was performed on a single crystal of **5a** grown by slow evaporation of the solvent from the crude reaction mixture in CH_2Cl_2/hexane 1 : 3. As already described in the literature for oxazolidines derived from dichloro olefins [8], also in the case of **5a** only one of the two possible epimers with *exo*-orientation of H–C(3) was detected. The formation of product **5a′** was observed after rearrangement of **5a** in the acidic medium, which was slowly generated in solution of **5a** in $CDCl_3$.

In the case of dibromo derivatives **4b** (*Entry 2*, *Table*), the ^{1}H-NMR spectrum of the crude reaction mixture exhibited three *doublet*s for the benzylic H-atoms of the oxazolidine ring at *ca.* 5 ppm. The ratio of the integrated signals was 80 : 7 : 13. In the same way as for **5a**, these *doublet*s were assigned to structures of **5b**, **5b′**, and **5b″**. Also in this case, the re-equilibrium from **5b** to **5b′** was detected by NMR analysis. Unfortunately, due to the poor crystallinity of the diasteroisomers **5b**, **5b′**, and **5b″**, all attempts to purify a sample by crystallization failed. Also, the use of standard chromatographic methods did not allow isolation of any pure sample of one diasteroisomer. The direct hydrolysis of the mixture of **b**-type oxazolidines using pyridinium *p*-toluenesulfate (PPTS) as acid in THF/H_2O, gave ketone **6b** in high yield. The diastereoisomer ratio **5b**/**5b′**/**5b″**, calculated by NMR integration of the crude mixture of products, provided an ee value of 74%, exactly matching, as described below, the value calculated by HPLC analysis.

The desymmetrization reaction of the *exo*-dibromo bicycle **4c** also gave three diastereoisomers (*Table*, *Entry 3*), but, in this case, the major diastereoisomer **5c** was successfully isolated by column chromatography in an almost pure state. The cleavage of the chiral auxiliary in **5c** furnished **6c** in 93% chemical yield and with 97% ee.

The tetrabromo compound **4d** exhibited the same reactivity as **4c** as indicated in the *Table* (*Entry 4*). In this case, the major diastereoisomer **5d** was purified by crystallization (Et_2O/hexane 9 : 1). Hydrolysis gave ketone **6d** as a single enantiomer in 88% chemical yield and > 99% ee. In this case, it is important to emphasize that the nucleophile reacted with only one of the two dibromo olefin sides present in the molecule. This reactivity is probably due to the steric hindrance induced by the oxozalidine ring of **5d** that prevents the entry of the second nucleophile at the other reactive site of **4d**.

Finally, the desymmetrization reaction was tested on *endo*-**4e**, but no oxazolidine products could be detected. This unexpected result is probably due to the steric hindrance exerted by the benzene moiety which is not present in the other olefins thus far employed. When the reaction temperature was raised up to 120°, three products

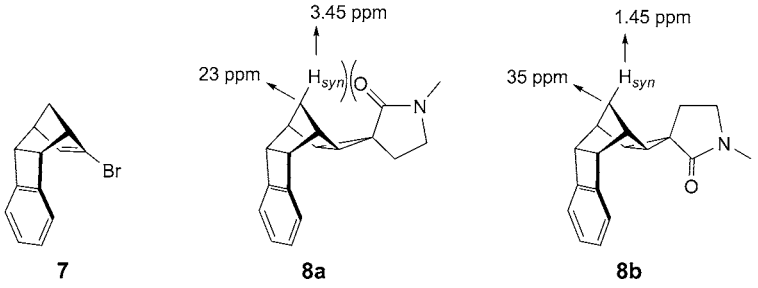


Figure. *Monobromo derivative* **7**, *and cyclopropanoid compounds* **8a** *and* **8b**

were isolated: monobromide **7**, and the cyclopropanoid compounds **8a** and **8b**. These two molecules are the reaction of NMP at **4e** (*Fig.*).

The relative configurations of the lactams **8a** and **8b** were determined by the chemical-shift variation of the atom H_{syn} and methano-C-atom. According to the γ-gauche effect in NMR spectroscopy [17], the H-atoms subjected to *Van der Waals* interactions are shifted to lower fields, whereas the *ipso*-C-atoms are shifted to higher fields. This effect is highlighted in conformationally rigid systems like the bicyclic structures of the present work. As indicated in the *Figure*, the signal of the atom H_{syn} of **8a** appears at δ(H) 1.45; however, at δ(H) 3.45 for **8b**. There is also a remarkable difference in the chemical shifts of the CH_2 C-atoms of compounds **8a** and **8b**, from δ(C) 23 to 35 ppm. In agreement with the observations mentioned above, we assigned the relative configurations of the lactams **8a** and **8b** as depicted in the *Figure*.

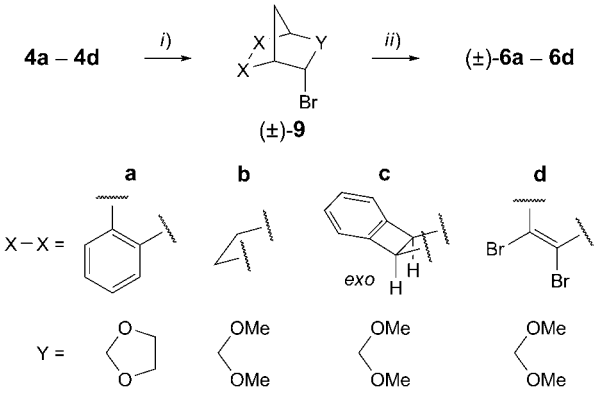
To determine the enantiomeric purity of the ketones **6a**–**6d** by HPLC, a sample of the racemate as reference standard was prepared using achiral alcohols in place of (−)-ephedrine. As shown in *Scheme 3*, ethylene glycol was used for **4a**, while MeOH was used for all other samples **4b**–**4d**, and, therefore, four acetals, (±)-**9a**–(±)-**9d**, and ketones, (±)-**6a**–(±)-**6d**, were synthesized. The analysis was carried out by employing a *Chiralcel AS-H*® column and hexane/^{i}PrOH 95:5 as mobile phase. The results are compiled in the *Table*.

The absolute configurations of **6a** and **6b** were determined by comparison of the optical rotations with those of the known compounds **10a** and **10b** [18][19], after removal the Br-atom using Zn/AcOH as reductant as shown in *Scheme 4*.

In the case of **10a**, the optical rotation found was $[\alpha]_D^{25} = +581$ ([18]: for (−)-stereoisomer $[\alpha]_D^{25} = -578$), while **10b** had a $[\alpha]_D^{25}$ value of +27 ([19]: $[\alpha]_D^{25} = +34$) [19]. These data established that the desymmetrization process proceeded as in the cases of the dichloro [8] and bis(phenylsulfonyl) norbornadienes [9] affording, with natural (−)-ephedrine, ketones with (*R*)-configuration at C(1).

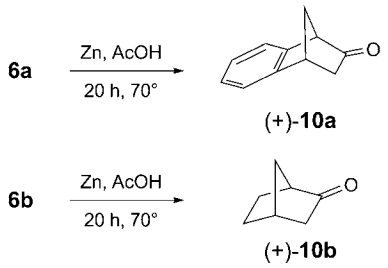
Conclusions. – In this work, four new norbornanoid oxazolidines, **5a**–**5d**, and the related α-bromoketones, **6a**–**6d**, were obtained through a three-steps synthesis in good yield, diastereoselectivity, and excellent enatioselectivity. Enantiomer purities of **6a**–**6d** were determined by HPLC analysis, and the absolute configurations of **6a** and **6b** were established.

Scheme 3



i) 2.2 equiv. of alcohols, 2.2 equiv. of ^{t}BuOK, NMP, 16 h, 80°. *ii*) 1M HCl, H_2O, THF, 2 d.

Scheme 4



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Experimental Part

General. TLC: Al-Backed silica-gel *60* F_{254} plates (SiO_2; *Merck*). Prep. TLC: SiO_2 *60* $HF_{254+366}$ (*Merck*). Column chromatography (CC): SiO_2 *60* (*Merck*); with hexane (b.p. 40 – 60°)/AcOEt. Enantiomeric excess (ee) was determined directly from the areas under the curve. Optical rotations: 589-nm spectropolarimeter at 25°. Polarimetric ee values were determined using HPLC analysis on a *Thermo Spectra Analysis HPLC System* equipped with a UV detector using a chiral column (*Chiralcel AS-H*); hexane/^{i}PrOH 95 : 5 as the eluent, a flow rate of 1.0 ml/min; the detection performed at a wavelength of 220 nm. IR Spectra: *Matson 1000* FT-IR spectrometer with KBr pellets; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian* or *Bruker* 400-MHz spectrometer in $CDCl_3$ unless stated otherwise; δ in ppm rel. to Me_4Si as internal standard; *J* in Hz. MS: *Varian 300 MS* (*TQ* mass spectrometer); in *m*/*z* (rel. %). Elemental analyses: *LECO CHNS-932* elemental analyzer.

General Procedure for the Reaction of 2,3-Dibromonorbornenes **4** *with Nucleophiles.* Amino alcoholate, or alcoholate, or diolate (1.5 equiv.), prepared *in situ* by reaction with base (3 equiv.), in dry NMP (*N*-methylpyrrolidin-2-one; 10 ml), was added to a soln. of 1.0 equiv. of dihalo olefin (**4a** – **4d**;

1.0 mmol) in dry NMP (5 ml). After 16 h at 80° (for **4e** 120° for 4 d) under Ar, the cooled mixture was treated with H_2O (20 ml) and extracted with pentane (3 × 20 ml); the combined org. layers were dried ($MgSO_4$), and the solvent was removed. Products **5a** and **5d** were purified by crystallization. Products **5b**, **5b'**, and **5b''** were used for the following reaction without purification. Product **5c** was purified by CC (hexane/AcOEt 95:5). Products **7**, **8a**, and **8b** were isolated by CC (hexane/AcOEt 96:4). Acetals (±)-**9a**, (±)-**9c**, and (±)-**9d** were purified by crystallization, whereas (±)-**9b** was purified by CC (hexane/AcOEt 95:5).

*(1*R*,2*S*,3*R*,4*S*,4′*S*,5′*R*)-3-Bromo-3,4-dihydro-3′,4′-dimethyl-5′-phenyl-1*H*-spiro[1,4-methanonaphthalene-2,2′-[1,3]oxazolidine]* (**5a**). Yield: 315 mg (82%). Colorless crystals (from hexane/CH_2Cl_2 3:1). M.p. 137–138°. $[\alpha]_D = +14$ ($c = 1.0$, $CHCl_3$). IR: 3746, 3024, 2978, 2932, 2798, 2874, 1471, 1459, 1291, 1260, 1057, 1043, 770, 750, 704. ^{1}H-NMR: 7.35–7.08 (*m*, 9 H); 5.00 (*d*, *J* = 8.2, 1 H); 4.75 (*d*, *J* = 4.2, 1 H); 3.55–3.53 (*m*, 2 H); 3.29 (*dq*, *J* = 8.2, 6.5, 1 H); 2.56 (*s*, 3 H); 2.21–2.20 (*m*, 2 H); 0.68 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR: 145.4; 144.4; 139.1; 128.0; 127.5; 127.3; 126.6; 125.5; 123.7; 122.6; 99.3; 80.3; 61.4; 56.4; 50.5; 46.3; 46.2; 34.4; 15.7. EI-MS: 385/383 (10, M^+), 304 (87, $[M - Br]^+$), 281 (14), 207 (23), 157 (34), 128 (100), 118 (47), 91 (32), 77 (11), 63 (6). Anal. calc. for $C_{21}H_{22}BrNO$: C 65.63, H 5.77, N 3.64; found: C 65.69, H 5.77, N 3.60.

*(1*S*,2*S*,3*R*,4*R*,4′*S*,5′*R*)-3-Bromo-3′,4′-dimethyl-5′-phenylspiro[bicyclo[2.2.1]heptane-2,2′-[1,3]oxazolidine]* (**5b**). Yield: 248 mg (73%). Pale-yellow wax. $[\alpha]_D = -67.5$ ($c = 0.4$, $CHCl_3$). IR: 3087, 3063, 3028, 2964, 2931, 2873, 2997, 1456, 1368, 1329, 1305, 1234, 1216, 1199, 1064, 1016, 758, 742, 721, 700. ^{1}H-NMR: 7.48–7.26 (*m*, 5 H); 4.96 (*d*, *J* = 8.5, 1 H); 4.46 (*dd*, *J* = 4.1, 2.1, 1 H); 3.06 (*dq*, *J* = 8.5, 6.5, 1 H); 2.50–2.47 (*m*, 2 H); 2.40 (*s*, 3 H); 1.91–1.89 (*m*, 1 H); 1.71 (br. *d*, *J* = 10.8, *A* part of *AB* system, 1 H); 1.55 (br. *d*, *J* = 10.8, *B* part of *AB* system, 1 H); 1.51–1.29 (*m*, 3 H); 0.60 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR: 139.6; 128.3; 128.0; 127.8; 97.7; 81.0; 61.3; 60.5; 43.5; 38.0; 36.6; 34.2; 24.3; 22.6; 16.1. GC/MS-MS (CI, 150 eV): 338/336 (25, $[M + H]^+$), 256 (75, $[M - Br]^+$), 176 (9), 148 (100), 118 (20), 81 (12), 58 (32). Anal. calc. for $C_{17}H_{22}BrNO$: C 60.72, H 6.59, N 4.17; found: C 61.71, H 6.57, N 4.50.

*(1′*S*,2*S*,2′*S*,4*S*,5*R*,9′*R*,10′*R*,12′*R*)-12′-Bromo-3,4-dimethyl-5-phenylspiro[1,3-oxazolidine-2,11′-tetracyclo[8.2.1.0^{2,9}.0^{3,8}]trideca[3,5,7]triene]* (**5c**). Yield: 298 mg (73%). Pale-yellow liquid. $[\alpha]_D = -78.21$ ($c = 3.35$, $CHCl_3$). IR: 3033, 3063, 2965, 2872, 2854, 2798, 1495, 1455, 1294, 1271, 1072, 1045, 750, 701. ^{1}H-NMR: 7.49–6.89 (*m*, 9 H); 5.09 (*d*, *J* = 8.5, 1 H); 4.59 (*d*, *J* = 4.0, 1 H); 3.93 (*d*, *J* = 3.7, 1 H); 3.84 (*d*, *J* = 3.7, 1 H); 3.15 (*dq*, *J* = 8.5, 6.5, 1 H); 2.60–2.57 (*m*, 2 H); 2.41 (*s*, 3 H); 1.46 (br. *d*, *J* = 11.8, *A* of *AB*, 1 H); 1.13 (*dt*, *J* = 11.8, 1.7, *B* of *AB*, 1 H); 0.66 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR: 145.3; 144.8; 139.3; 128.1; 127.9; 127.7 (3×); 122.4; 122.2; 97.8; 80.9; 61.2; 58.3; 44.8; 44.4; 43.8; 38.0; 34.1; 30.3; 15.9. GC/MS-MS (CI, 150 eV): 412/410 (28, $[M + H]^+$), 330 (98, $[M - Br]^+$), 267 (8), 202 (16), 148 (100), 107 (28), 58 (40). Anal. calc. for $C_{23}H_{24}BrNO$: C 67.32, H 5.90, N 3.41; found: C 67.55, H 5.92, N 3.42.

*(1*S*,2*S*,3*R*,4*R*,4′*S*,5′*R*)-3,5,6-Tribromo-3′,4′-dimethyl-5′-phenylspiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]oxazolidine]* (**5d**). Yield: 363 mg (74%). Colorless crystals (from Et_2O/hexane 9:1). M.p. 151–153°. $[\alpha]_D = +2.0$ ($c = 1$, $CHCl_3$). IR: 3128, 3027, 2963, 1404, 1260, 1104, 800, 615. ^{1}H-NMR: 7.47–7.45 (*m*, 2 H); 7.32–7.22 (*m*, 3 H); 5.11 (*d*, *J* = 8.3, 1 H); 4.56 (*d*, *J* = 3.2, 1 H); 3.29–3.20 (*m*, 3 H); 2.42 (*s*, 3 H); 2.33 (*dt*, *J* = 10.0, 1.7, *A* of *AB*, 1 H) 1.91 (*dt*, *J* = 10.0, 1.5, *B* of *AB*, 1 H); 0.69 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR: 139.1; 128.3; 128.2; 128.0; 127.9; 125.2; 100.8; 81.6; 61.5; 56.31; 53.6; 53.1; 46.1; 34.3; 15.8. EI-MS: 493/491/489/495 (100, $[M + H]^+$), 416/414/412 (8, $[M - Br]^+$), 148 (72). Anal. calc. for $C_{17}H_{18}Br_3NO$: C 41.50, H 3.69, N 2.85; found: C 41.15, H 3.66, N 2.81.

rac-*(1′R,3′R,4′S)-3′-Bromo-3′,4′-dihydro-1′*H*-spiro[1,3-dioxolane-2,2′-[1,4]methanonaphthalene]* (**9a**). Yield: 240 mg (85%). Colorless crystals (from Et_2O/hexane 9:1). M.p. 105–107°. IR: 2967, 2882, 1463, 1402, 1291, 1262, 1197, 1163, 1098, 1035, 1003, 800, 765. ^{1}H-NMR: 7.28–7.17 (*m*, 4 H); 4.44–4.43 (*m*, 1 H); 4.06–4.00 (*m*, 1 H); 3.96–3.90 (*m*, 3 H); 3.50–3.47 (*m*, 1 H); 3.19–3.17 (*m*, 1 H); 2.25–2.23 (*m*, 2 H). ^{13}C-NMR: 144.3; 142.9; 127.1; 126.5; 124.2; 123.5; 133.0; 66.2; 64.9; 59.7; 52.4; 50.3; 47.0. GC/MS-MS (CI, 150 eV): 283/281 (13, $[M + H]^+$), 240/239 (65), 202/201 (85, $[M - Br]^+$), 157 (51), 129 (63), 116 (38), 73 (100), 51 (15). Anal. calc. for $C_{13}H_{13}BrO_2$: C 55.54, H 4.66; found: C 55.62, H 4.52.

rac-*(1*R*,3*S*,4*S*)-3-Bromo-2,2-dimethoxybicyclo[2.2.1]heptane* (**9b**). Yield: 202 mg (86%). Pale-yellow wax. IR: 2961, 2876, 2833, 1454, 1331, 1198, 1171, 1132, 1090, 1058, 1031, 968, 763. ^{1}H-NMR: 4.16 (*d*, *J* = 3.9, 1 H); 3.25 (*s*, 3 H); 3.20 (*s*, 3 H); 2.48–2.45 (*m*, 1 H); 2.36–2.34 (*m*, 1 H); 1.90–1.81 (*m*, 1 H); 1.75 (br. *d*, *J* = 10.4, *A* of *AB*, 1 H); 1.55 (br. *d*, *J* = 10.4, *B* of *AB*, 1 H); 1.44–1.27 (*m*, 3 H).

^{13}C-NMR: 104.3; 58.7; 51.0; 47.8; 43.6; 43.3; 35.0; 23.2; 21.8. GC/MS-MS (CI, 150 eV): 205/203 (23, [*M* – MeO]$^+$), 125 (100, [*M* – Br – MeO]$^+$), 93 (52, [*M* – Br – 2 MeO]$^+$), 67 (6). Anal. calc. for $C_9H_{15}BrO_2$: C 45.98, H 6.43; found: C 45.63, H 6.79.

rac-*(1*R*,2*R*,9*S*,10*S*,12*S*)-12-Bromo-11,11-dimethoxytetracyclo[8.2.1.0^{2,9}.0^{3,8}]trideca-3,5,7-triene* (**9c**). Yield: 266 mg (86%). Colorless crystals (from Et_2O/hexane 9:1). M.p. 82–84°. IR: 2963, 2833, 1455, 1261, 1160, 1123, 1050, 801, 759, 615. ^{1}H-NMR: 7.25–7.20 (*m*, 2 H); 7.05–6.99 (*m*, 2 H); 4.30 (*d*, *J* = 4.4, 1 H); 3.87 (*d*, *J* = 3.3, 1 H); 3.47 (*d*, *J* = 3.3, 1 H); 3.39 (*s*, 3 H); 3.26 (*s*, 3 H); 2.60–2.58 (*m*, 1 H); 2.47–2.45 (*m*, 1 H); 1.53 (br. *d*, *J* = 11.3, *A* of *AB*, 1 H); 1.10 (br. *d*, *J* = 11.3, *B* of *AB*, 1 H). ^{13}C-NMR: 145.6; 144.3; 128.0; 128.0; 122.6; 122.4; 104.5; 57.6; 51.5; 48.5; 45.2; 43.8; 43.8; 42.9; 29.5. EI-MS: 310/308 (3, M^+), 277/275 (3, [*M* – MeO]$^+$), 229 (100, [*M* – Br]$^+$), 165 (29, [*M* – Br – 2 MeO]$^+$), 153 (35, [*M* – Br – 2 MeO – CH_2]$^+$), 141 (48), 101 (54), 76 (11). Anal. calc. for $C_{15}H_{17}BrO_2$: C 58.27, H 5.54; found: C 57.88, H 5.60.

rac-*(1*R*,4*S*,6*R*)-2,3,6-Tribromo-5,5-dimethoxybicyclo[2.2.1]hept-2-ene* (**9d**). Yield: 313 mg (80%). Colorless crystals (from Et_2O/hexane 9:1). M.p. 88–90°. IR: 2944, 2850, 1594, 1451, 1170, 1144, 1118, 1068, 1048, 873. ^{1}H-NMR: 4.34 (*d*, *J* = 3.5, 1 H); 3.42 (*s*, 3 H); 3.31 (*s*, 3 H); 3.26–3.23 (*m*, 1 H); 3.16–3.15 (*m*, 1 H); 2.31 (*dt*, *J* = 9.5, 2.0, *A* of *AB*, 1 H); 1.95 (*dt*, *J* = 9.5, 1.6, *B* of *AB*, 1 H). ^{13}C-NMR: 127.2; 124.5; 106.5; 56.9; 56.3; 53.3; 52.4; 50.1; 46.6. GC/MS-MS (CI, 150 eV): 394/393/390/388 (3, M^+), 361 (83, [*M* – MeO]$^+$), 313/311/309 (16, [*M* – Br]$^+$), 279 (11, [*M* – Br – MeO]$^+$), 233/231 (33, [*M* – 2 Br]$^+$), 201 (7, [*M* – 2 Br – MeO]$^+$), 168/166 (100, [*M* – 2 Br – 2 MeO]$^+$), 87/85 (19, [*M* – 3 Br – 2 MeO]$^+$), 75 (33, [*M* – 3 Br – 2 MeO – CH_2]$^+$), 75 (35). Anal. calc. for $C_9H_{11}Br_3O_2$: C 27.65, H 2.84; found: C 28.03, H 3.14.

rac-*(1*R*,2*R*,9*R*,10*S*)-11-Bromotetracyclo[8.2.1.0^{2,9}.0^{3,8}]trideca-3,5,7,11-tetraene* (**7**; first fraction) [11c]. Yield: 101 mg (41%). Colorless crystals (from hexane). M.p. 51°. IR: 3063, 2986, 2940, 2870, 1587, 1452, 1317, 1279, 1247, 1138, 1003, 933, 817, 759. ^{1}H-NMR: 7.19–6.94 (*m*, 4 H); 5.73 (*d*, *J* = 3.1, 1 H); 3.91 (*t*, *J* = 4.7, 1 H); 3.74 (*t*, *J* = 4.7, 1 H); 3.10 (br. *d*, *J* = 4.7, 1 H); 3.01–3.00 (*m*, 1 H); 2.22 (br. *d*, *J* = 8.5, *A* of *AB*, 1 H), 1.70 (br. *d*, *J* = 8.5, *B* of *AB*, 1 H). ^{13}C-NMR: 147.0; 146.4; 132.3; 127.0; 126.6; 123.7; 122.4; 122.3; 54.3; 52.0; 47.0; 45.8; 44.7.

rac-*(1*R*,2*R*,9*S*,10*S*,11*S*,13*R*)-1′-Methyl-2′*H*-spiro[pentacyclo[8.3.1.0^{2,9}.0^{3,8}.0^{11,13}]tetradeca-3,5,7-triene-12,3′-pyrrolidin]-2′-one* (**8a**; second fraction). Yield: 93 mg (35%). Colorless crystals (from hexane/CH_2Cl_2 4:1). M.p. 92–93°. IR: 3035, 3003, 2949, 2890, 1677, 1453, 1397, 1089, 733. ^{1}H-NMR: 7.14–6.99 (*AA′BB′*, 4 H); 3.62 (br. *d*, *J* = 4.5, 2 H); 3.46 (*dt*, *J* = 10.7, 1.6, *A* of *AB*, 1 H); 3.16 (*t*, *J* = 6.7, 2 H); 2.82 (*s*, 3 H); 2.74–2.73 (*m*, 2 H); 1.51 (*t*, *J* = 6.7, 2 H); 1.15 (br. *d*, *J* = 10.7, *B* of *AB*, 1 H). ^{13}C-NMR: 176.0; 146.6; 126.9; 123.3; 50.2; 46.8; 36.8; 36.2; 29.9; 26.4; 26.3; 23.2. EI-MS: 265/264 (25, M^+), 178 (45), 165 (50), 154 (45), 141 (100), 136 (80), 128 (63), 115 (53). Anal. calc. for $C_{18}H_{19}NO$: C 81.47, H 7.22, N 5.28, found: C 81.38, H 7.20, N 5.41.

rac-*(1*R*,2*R*,9*S*,10*S*,11*S*,13*R*)-1′-Methyl-2′*H*-spiro[pentacyclo[8.3.1.0^{2,9}.0^{3,8}.0^{11,13}]tetradeca-3,5,7-triene-12,3′-pyrrolidin]-2′-one* (**8b**; third fraction). Yield: 45 mg (17%). Colorless liquid. IR: 3061, 3029, 2955, 2786, 1688, 1683, 1504, 1471, 1454, 1435, 1402, 1318, 1302, 1293, 1247, 1138, 1094, 759, 732, 711. ^{1}H-NMR: 7.16–7.00 (*AA′BB′*, 4 H); 3.65–3.62 (*m*, 2 H); 3.35–3.32 (*m*, 2 H); 2.72 (*s*, 3 H); 2.59–2.57 (*m*, 2 H); 2.18–2.15 (*m*, 2 H); 1.45 (br. *d*, *J* = 11.0, *A* of *AB*, 1 H); 1.18 (br. *d*, *J* = 11.0, *B* of *AB*, 1 H); 0.89–0.87 (*m*, 2 H). ^{13}C-NMR: 175.3; 147.8; 126.4; 123.2; 51.0; 46.0; 38.2; 35.9; 35.0; 32.6; 30.7; 29.3. EI-MS: 265/264 (30, M^+), 178 (50), 165 (58), 154 (40), 141 (100), 136 (75), 128 (87), 102 (62), 77 (45). Anal. calc. for $C_{18}H_{19}NO$: C 81.47, H 7.22, N 5.28; found: C 81.25, H 7.38, N 5.28.

General Procedure for the Synthesis of Racemic Ketones **6a**–**6d**. A soln. of **5** (0.76 mmol) and PPTS (pyridinium *p*-toluenesulfonate; 190 mg, 0.76 mmol) in THF (5 ml) and H_2O (5 ml) was stirred at r.t. for 2 d and then diluted with H_2O (20 ml) and extracted with pentane (3 × 20 ml). The combined org. layers were dried ($MgSO_4$). The crude reaction product was purified by crystallization or CC. The same procedure was performed for hydrolyses of acetals **9** using 1M HCl instead of PPTS.

*(1*R*,3*R*,4*S*)-3-Bromo-3,4-dihydro-1,4-methanonaphthalen-2(1*H*)-one* (**6a**). Yield: 180 mg (100%). Colorless crystals (from hexane/CH_2Cl_2 4:1). M.p. 59–60°. $[\alpha]_D = +311.5$ (*c* = 1, $CHCl_3$). IR: 3071, 3044, 2947, 2873, 1797, 1752, 1460, 1308, 1273, 1121, 987, 808. ^{1}H-NMR: 7.40–7.17 (*m*, 4 H); 4.51 (*d*, *J* = 4.5, 1 H); 3.80–3.78 (*m*, 1 H); 3.75–3.73 (*m*, 1 H); 2.76 (*ddd*, *J* = 10.4, 2.4, 1.4, *A* of *AB*, 1 H); 2.43 (*dt*, *J* = 10.4, 1.4, *B* of *AB*, 1 H). ^{13}C-NMR: 205.9; 144.9; 138.7; 127.8; 127.4; 124.6; 123.3; 48.6; 48.2; 47.8; 43.5.

GC/MS-MS (CI, 150 eV): 239/237 (23, $[M+H]^+$), 157 (83, $[M-Br]^+$), 129 (100), 115 (10), 64 (5). Anal. calc. for $C_{11}H_9BrO$: C 55.72, H 3.83; found: C 55.52, H 4.22.

(1S,3R,4R)-3-Bromobicyclo[2.2.1]heptan-2-one (**6b**). Yield: 144 mg (100%). Pale-yellow wax. $[\alpha]_D = -46.96$ ($c = 0.58$, $CHCl_3$). IR: 2969, 2879, 1755, 1450, 1402, 1294, 1157, 1076, 941, 781. ^{1}H-NMR: 4.33 (*d*, *J* = 4.3, 1 H); 2.85–2.82 (*m*, 1 H); 2.75 (*d*, *J* = 4.9, 1 H); 2.10–2.02 (*m*, 1 H); 1.92–1.82 (*m*, 3 H); 1.78–1.70 (*m*, 1 H); 1.59–1.52 (*m*, 1 H). ^{13}C-NMR: 210.2; 55.1; 48.2; 42.2; 35.3; 25.0; 22.7. GC/MS-MS (CI, 150 eV): 191/189 (12, $[M+H]^+$), 109 (20, $[M-Br]^+$), 81 (100, $[M-Br-CO]^+$), 67 (8). Anal. calc. for C_7H_9BrO: C 44.47, H 4.80; found: C 44.83, H 5.16.

(1S,2S,9R,10R,12R)-12-Bromotetracyclo[8.2.1.0^{2,9}.0^{3,8}]trideca-3,5,7-trien-11-one (**6c**). Yield: 200 mg (100%). Colorless crystals (from hexane/CH_2Cl_2 4:1). M.p. 88–89°. $[\alpha]_D = +236.36$ ($c = 0.11$, $CHCl_3$). IR: 2958, 1760, 1456, 1280, 1143, 731. ^{1}H-NMR: 7.30–7.26 (*m*, 2 H); 7.10–7.05 (*m*, 2 H); 4.43 (*d*, *J* = 4.5, 1 H); 4.08 (*d*, *J* = 3.6, 1 H); 3.53 (*d*, *J* = 3.6, 1 H); 2.94–2.93 (*m*, 1 H); 2.87 (*s*, 1 H); 1.68 (br. *d*, *J* = 11.8, *A* of *AB*, 1 H); 1.49 (br. *d*, *J* = 11.8, *B* of *AB*, 1 H). ^{13}C-NMR: 207.9; 144.6; 141.0; 128.7; 128.6; 122.9; 122.3; 53.1; 49.1; 45.0; 44.0; 41.8; 29.8. GC/MS-MS (CI, 150 eV): 265/263 (15, $[M+H]^+$), 183 (92, $[M-Br]^+$), 165 (12), 155 (100, $[M-Br-CO]^+$), 142 (28), 115 (10), 55 (25). Anal. calc. for $C_{13}H_{11}BrO$: C 59.34, H 4.21; found: C 59.49, H 4.30.

(1S,3R,4R)-3,5,6-Tribromobicyclo[2.2.1]hept-5-en-2-one (**6d**). Yield: 262 mg (100%). Colorless crystals (from Et_2O/hexane 9:1). M.p. 142–143°. $[\alpha]_D = +201.0$ ($c = 0.15$, $CHCl_3$). IR: 2963, 2927, 2855, 1767, 1739, 1582, 1449, 1412, 1261, 1026, 864, 802. ^{1}H-NMR: 4.31 (*d*, *J* = 3.4, 1 H); 3.54–3.52 (*m*, 1 H); 3.35–3.34 (*m*, 1 H); 2.89 (*ddd*, *J* = 10.3, 2.5, 1.6, *A* of *AB*, 1 H); 2.22 (*dt*, *J* = 10.3, 1.6, *B* of *AB*, 1 H). ^{13}C-NMR: 202.8; 131.5; 121.4; 61.7; 53.9; 47.7; 44.1. EI-MS: 348/346/344/342 (29, M^+), 265 (13, $[M-Br]^+$), 239/237/235 (40, $[M-Br-CO]^+$), 226/224 (100), 207 (36), 158/156 (64, $[M-2\,Br-CO]^+$), 145/143 (45, $[M-2\,Br-CO-CH_2]^+$), 77 (30, $[M-3\,Br-CO]^+$). Anal. calc. for $C_7H_5Br_3O$: C 24.38, H 1.46; found: C 24.29, H 1.46.

General Procedure for the Reduction of Bromo Ketones **6a** *and* **6b**. To a vigorously stirred suspension of Zn dust (2.0 g, 0.03 mol) in 5 ml of glacial AcOH, a soln. of bromo ketone (0.42 mmol) in 2 ml of glacial AcOH was added dropwise. After addition was complete, the temp. was raised to and maintained at 70° for 20 h. The soln. was then cooled and filtered through *Celite*. The solvent was evaporated *in vacuo*, CH_2Cl_2 (30 ml) was added to the residue, and org. layer was washed with H_2O (2 × 10 ml) and dried on $CaCl_2$.

(1R,4R)-3,4-Dihydro-1,4-methanonaphthalen-2(1H)-one (**10a**). Yield: 50 mg (74%). Colorless wax. $[\alpha]_D = +581$ ($c = 0.76$, $CHCl_3$). ^{1}H-NMR: 7.28–7.09 (*m*, 4 H); 3.67–3.64 (*m*, 1 H); 3.57–3.56 (*m*, 1 H); 2.46 (*ddt*, *J* = 9.6, 4.6, 1.7, *A* of *AB*, 1 H); 2.30 (*dd*, *J* = 17.0, 3.9, *A* of *AB*, 1 H); 2.26 (*dt*, *J* = 9.6, 1.3, *B* of *AB*, 1 H); 1.96 (*dd*, *J* = 17.0, 4.5, *B* of *AB*, 1 H). ^{13}C-NMR: 213.6; 148.8; 140.0; 127.6; 126.9; 123.8; 121.7; 58.2; 51.0; 41.9; 40.5.

(1S,4R)-Bicyclo[2.2.1]heptan-2-one (**10b**). Yield: 36 mg (78%). Yellowish wax. $[\alpha]_D = +36.59$ ($c = 0.41$, $CHCl_3$; 74% ee). ^{1}H-NMR: 2.68–2.65 (*m*, 1 H); 2.61–2.58 (*m*, 1 H); 2.06 (br. *d*, *J* = 15.6, 1 H); 1.86–1.72 (*m*, 4 H); 1.57–1.39 (*m*, 3 H). ^{13}C-NMR: 218.3; 49.9; 45.3; 37.7; 35.3; 27.2; 24.2.

REFERENCES

[1] E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, N. M. Weinshenker, *J. Am. Chem. Soc.* **1970**, *92*, 397; E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675.

[2] H. Miyaoka, Y. Isaji, H. Mitome, Y. Yamada, *Tetrahedron* **2003**, *59*, 61.

[3] S. Chiba, M. Kitamura, K. Narasaka, *J. Am. Chem. Soc.* **2006**, *128*, 6931.

[4] P. C. Belanger, I. J. Collins, J. C. Hannam, T. Harrison, S. J. Lewis, A. Madin, E. G. Mc Iver, A. J. Nadin, J. G. Neduvelil, M. S. Shearman, A. L. Smith, T. J. Sparey, G. I. Stevenson, M. R. Teall, WO 01/70677A1, 2001.

[5] M. Muthuppalaniappan, G. Balasubramanian, S. Gullapalli, N. K. Joshi, S. Narayanan, US 2008 0234259A1, 2008.

[6] K. Hilpert, F. Hubler, D. Renneberg, WO2010/46855, 2010; L. Liu, N. Ishida, M. Murakami, *Angew. Chem., Int. Ed.* **2012**, *51*, 2485.

[7] a) S. Tartaggia, O. De Lucchi, A. Gambaro, R. Zangrando, F. Fabris, A. Scarso, *Chem. – Eur. J.* **2013**, *19*, 5701; b) F. Fabris, O. De Lucchi, I. Nardini, M. Crisma, A. Mazzanti, S. A. Mason, M.-H. Lemee-Cailleau, F. A. Scaramuzzo, C. Zonta, *Org. Biomol. Chem.* **2012**, *10*, 2464; c) F. Fabris, C. Zonta, G. Borsato, O. De Lucchi, *Acc. Chem. Res.* **2011**, *44*, 416; d) S. Tartaggia, A. Scarso, P. Padovan, O. De Lucchi, F. Fabris, *Org. Lett.* **2009**, *11*, 3926; e) G. Mazzeo, E. Giorgio, C. Rosini, F. Fabris, E. Fregonese, U. Toniolo, O. De Lucchi, *Chirality* **2009**, *21*, E86; f) E. Dalkiliç, M. Güney, A. Daştan, N. Saraçoğlu, O. De Lucchi, F. Fabris, *Tetrahedron Lett.* **2009**, *50*, 1989; g) A. Scarso, L. Pellizzaro, O. De Lucchi, A. Linden, F. Fabris, *Angew. Chem., Int. Ed.* **2007**, *46*, 4972; h) F. Fabris, L. Pellizzaro, C. Zonta, O. De Lucchi, *Eur. J. Org. Chem.* **2007**, 283; i) C. Zonta, F. Fabris, O. De Lucchi, *Org. Lett.* **2005**, *7*, 1003; j) G. Borsato, M. Crisma, O. De Lucchi, V. Lucchini, A. Zambon, *Angew. Chem., Int. Ed.* **2005**, *44*, 7435; k) G. Borsato, S. Brussolo, M. Crisma, O. De Lucchi, V. Lucchini, A. Zambon, *Synlett* **2005**, 1125; l) F. Fabris, L. Zambrini, E. Rosso, O. De Lucchi, *Eur. J. Org. Chem.* **2004**, 3313; m) O. De Lucchi, A. Daştan, A. Altundaş, F. Fabris, M. Balci, *Helv. Chim. Acta* **2004**, *87*, 2364; n) F. Fabris, L. Bellotto, O. De Lucchi, *Tetrahedron Lett.* **2003**, *44*, 1211; o) G. Borsato, O. De Lucchi, F. Fabris, V. Lucchini, M. Pasqualotti, A. Zambon, *Tetrahedron Lett.* **2003**, *44*, 561; p) G. Borsato, O. De Lucchi, F. Fabris, L. Groppo, V. Lucchini, A. Zambon, *J. Org. Chem.* **2002**, *67*, 7894; q) L. Zambrini, F. Fabris, O. De Lucchi, G. Gardenal, F. Visentin, L. Canovese, *Tetrahedron* **2001**, *57*, 8719; r) F. Fabris, A. De Martin, O. De Lucchi, *Tetrahedron Lett.* **1999**, *40*, 9121.

[8] S. Tartaggia, P. Padovan, G. Borsato, O. De Lucchi, F. Fabris, *Tetrahedron Lett.* **2011**, *52*, 4478.

[9] H. Sakurai, T. Daiko, T. Hirao, *Science* **2003**, *301*, 1878.

[10] S. Higashibayashi, H. Sakurai, *J. Am. Chem. Soc.* **2008**, *130*, 8592; S. Higashibayashi, A. F. G. M. Reza, H. Sakurai, *J. Org. Chem.* **2010**, *75*, 4626; S. Higashibayashi, R. B. N. Baig, Y. Morita, H. Sakurai, *Chem. Lett.* **2012**, *41*, 84 – 86; S. Higashibayashi, H. Sakurai, A. F. G. M. Reza, *Chem. Asian J.* **2009**, *4*, 1329.

[11] a) M. E. Şengül, D. D. Gültekin, S. Eşsiz, E. Şahin, A. Daştan, *Tetrahedron* **2009**, *65*, 4859; b) A. Daştan, *J. Chem. Res., Synop.* **2006**, 104; c) A. Daştan, E. Uzundumlu, M. Balci, F. Fabris, O. De Lucchi, *Eur. J. Org. Chem.* **2004**, 183; d) A. Daştan, F. Fabris, O. De Lucchi, M. Guney, M. Balci, *Helv. Chim. Acta* **2003**, *86*, 3411; e) A. Daştan, E. Uzundumlu, M. Balci, *Helv. Chim. Acta* **2002**, *85*, 2729; f) R. Altundaş, A. Daştan, N. S. Ünaldi, K. Güven, O. Uzun, M. Balci, *Eur. J. Org. Chem.* **2002**, 526; g) A. Altundaş, A. Daştan, M. M. McKee, M. Balci, *Tetrahedron* **2000**, *56*, 6115; h) Eşsiz, M. E. Şengül, E. Şahin, A. Daştan, *Turk. J. Chem.* **2011**, *35*, 587.

[12] G. Borsato, A. Linden, O. De Lucchi, V. Lucchini, D. Wolstenholme, A. Zambon, *J. Org. Chem.* **2007**, *72*, 4272.

[13] S. Cossu, P. Peluso, *Tetrahedron Lett.* **2006**, *47*, 4015; R. Ballini, G. Bosica, S. Cossu, O. De Lucchi, P. Peluso, *Tetrahedron* **2001**, *57*, 4461; S. Cossu, O. De Lucchi, P. Peluso, R. Volpicelli, *Tetrahedron Lett.* **2000**, *41*, 7263; F. Chéry, P. Rollin, O. De Lucchi, S. Cossu, *Tetrahedron Lett.* **2000**, *41*, 2357; S. Cossu, O. De Lucchi, P. Peluso, R. Volpicelli, *Tetrahedron Lett.* **1999**, *40*, 8705; S. Cossu, O. De Lucchi, P. Pasetto, *Angew. Chem., Int. Ed.* **1997**, *36*, 1504.

[14] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2007**, *41*, 40.

[15] B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.

[16] K. Hermann, S. Sardini, Y. Ruan, R. J. Yoder, M. Chakraborty, S. Vyas, C. M. Hadad, J. D. Badjić, *J. Org. Chem.* **2013**, *78*, 2984.

[17] C. Kazaz, A. Daştan, M. Balcı, *Magn. Reson. Chem.* **2005**, *43*, 75; M. D. Gheorghiu, E. Olteanu, *J. Org. Chem.* **1987**, *52*, 5158.

[18] H. L. Goering, J. V. Clevenger, K. Humski, *J. Org. Chem.* **1972**, *37*, 3019.

[19] E. Plettner, A. Mohle, M. T. Mwangi, J. Griscti, B. O. Patrick, R. Nair, R. J. Batchelor, F. Einstein, *Tetrahedron: Asymmetry* **2005**, *16*, 2754.

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