Pergamon

Tetrahedron, Vol. 52, No. 31, pp. 10473-10484, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00582-0

Asymmetric Synthesis of (2*R*)- and (2*S*)-2-Iodohexadecanal, Natural Inhibitors of the Thyroid Gland Metabolism

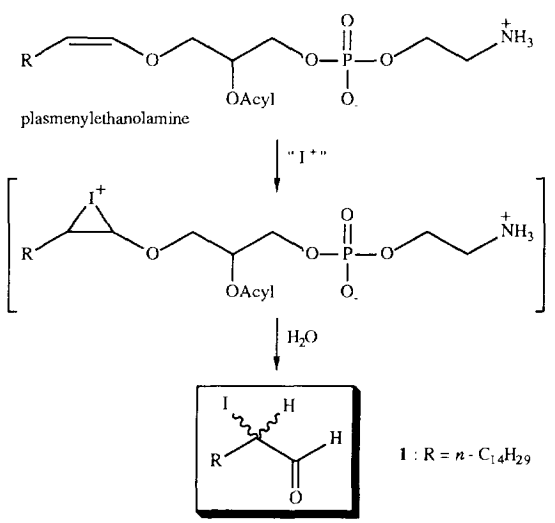
Claude Jacoby, Jean-Claude Braekman,* and Désiré Daloze

Laboratory of Bio-organic Chemistry (CP 160/7), Faculty of Sciences, University of Brussels
50 Av. F. D. Roosevelt, B-1050 Brussels, Belgium. Fax: 32.2.650.27.98

Abstract: (2*R*)-(+)- and (2*S*)-(-)-2-iodohexadecanal **1** with ee's ≥ 89% were synthesized in five steps and 62% overall yield from chiral enol ethers *Z*- and/or *E*-**7**, *via* the iodocyclization with ICl and chromatographic separation of the resulting diastereomeric 1'-iododioxanes **8**. The ee's of (2*S*)- and (2*R*)-**1** have been determined after their transformation to the (*R*)-*O*-methylmandelate esters **11** and **12** or to the epoxides (2*R*)- and (2*S*)-**13**, respectively. Their absolute configuration has been assigned through chemical correlation with **13** and by application of Mosher's method to the esters **15** and **16** obtained by methanolysis of (2*R*)- and (2*S*)-**13**, respectively, followed by derivatization. Moreover, the biosynthesis and the inhibitory activity of **1** have been shown to be unstereoselective.

INTRODUCTION

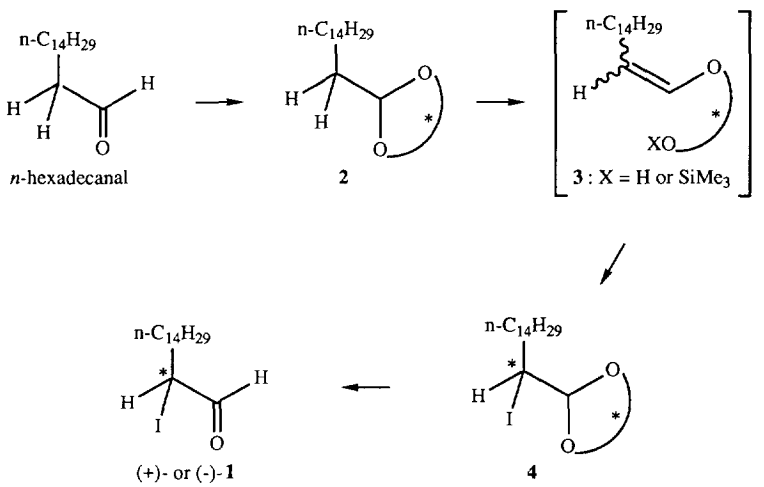
As part of a program dealing with the regulation mechanism of the thyroid gland metabolism by iodide, 2-iodohexadecanal (**1**) has been identified as a major iodolipid which can be formed upon addition of iodine to the vinyl ether group of plasmalogens followed by hydrolysis (Scheme 1).[1] The investigation of the biological



Scheme 1. *In vivo* formation of 2-iodoaldehydes by plasmalogen iodination.

activities of synthetic (±)-**1** revealed its ability to inhibit the H_2O_2 production in cultured dog thyroid cells[2a] as well as the human thyroid adenylyl cyclase.[2b]

These interesting results prompted us to study the influence of the absolute configuration of **1** on its biological properties and to determine whether the natural product was racemic or not. To this end, the asymmetric synthesis of both enantiomers of **1** had to be carried out. Up to now, only two methods for the preparation of nonracemic 2-halogenoaldehydes were available. The more efficient one is based on the stereo- and regioselective opening of an optically pure epoxyalcohol by a halide, the scalemic 2-iodo-, 2-bromo- and 2-chloroaldehyde being generated *via* the oxidative cleavage of the resulting 1,2-diol.[3a] The other one allows the asymmetric synthesis of 2-bromopropanal, through the diastereoselective bromination of the dimethyltartrate-derived dioxolane. However, poor optical and chemical yields were obtained.[3b] We nevertheless decided to use the latter approach, because of the possibility to take advantage of the numerous C_2 symmetrical diols available as chiral auxiliaries (Scheme 2).[4]

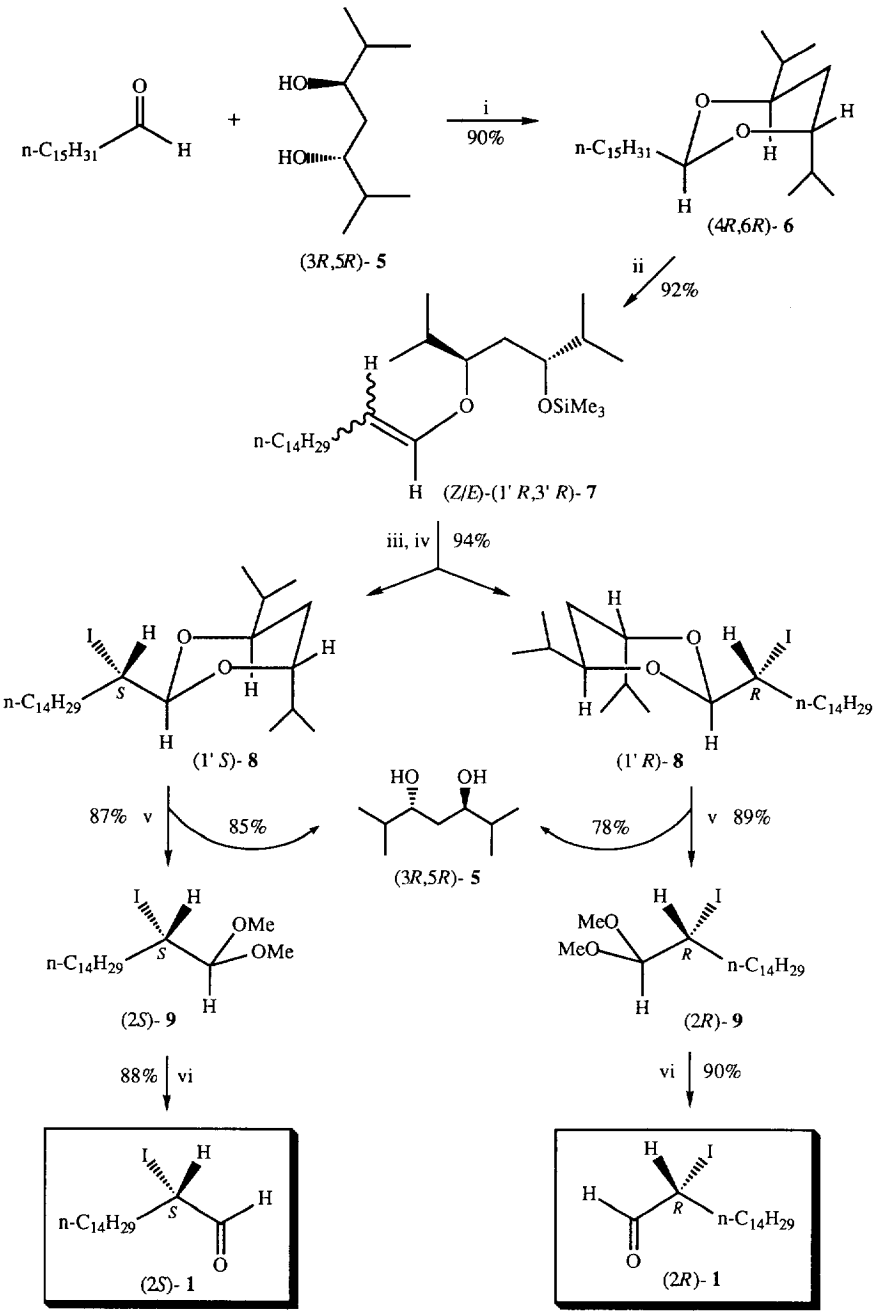


Scheme 2. Strategy used for the synthesis of (+)- and (-)-**1**.

RESULTS AND DISCUSSION

According to scheme 2, we first tried L-(+)-diisopropyltartrate {L-(+)-DIPT} as a chiral inductor. Unfortunately, the lack of diastereoselectivity for the iodination step of **2** {$HgCl_2$ (0.5 eq.)/I_2 (1.0 eq.)/$MeSO_3H$ (0.1 eq.)/CH_2Cl_2/r.t.; yield: 71%; de: 0%} coupled to the difficulty to enhance the diastereoisomeric excess of **4** by chromatography precluded the use of DIPT to achieve our goal. We assumed that the bad stereoselectivity was due to the unselective formation and/or to the absence of diastereoface discrimination during the iodination of the two possible intermediary enol ethers **3** resulting from opening of the acetal ring of **2**. Thus, we decided to perform the iodination on a diastereomerically pure and isolated vinyl ether obtained by treatment of the parent acetal **2** with a Lewis acid and a Brönsted base. However, neither Al(*i*-Bu)$_3$[5] nor TMSOTf/*i*-Pr$_2$NEt [6] proved efficient to accomplish the desired reaction on the dioxolane **2** deriving from L-(+)-DIPT.

Contrary to these results, the 1,3-dioxane (4*R*,6*R*)-**6**, formed by condensation of *n*-hexadecanal and (3*R*,5*R*)-2,6-dimethylheptane-3,5-diol[7] [(3*R*,5*R*)-**5**] in a 90% yield, was cleanly converted to the *Z* and *E* enol ethers (1'*R*,3'*R*)-**7** (92% yield), the *Z* isomer being the more abundant (*Z*/*E* ~ 5.0) (Scheme 3). This reaction worked well only if the reagent ratio (base/Lewis acid/acetal : 3.2/3.0/1.0) was higher than the one used in the



Reagents : i. *p*-TsOH / C_6H_6 / ΔT; ii. TMSOTf / *i*-Pr_2NEt / CH_2Cl_2 / 0°C → r.t.; iii. ICl / THF / -60°C; iv. flash chromatography on silica gel; v. *p*-TsOH / MeOH / ΔT; vi. CF_3CO_2H 70% / CH_2Cl_2 / 0°C.

Scheme 3. Asymmetric synthesis of (2*S*)- and (2*R*)-**1** using (3*R*,5*R*)-2,6-dimethylheptane-3,5-diol.

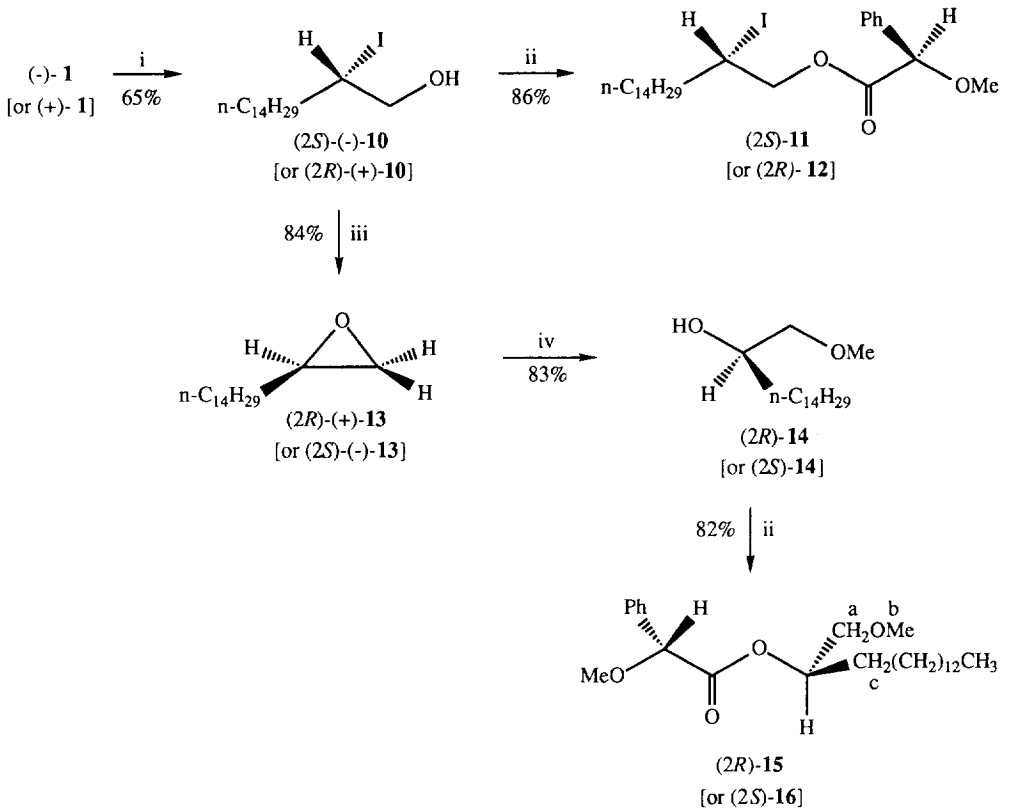
original procedure.[6,8] Moreover, the *Z* and *E* isomers were easily separable by flash chromatography on silica gel, with the result that pure *Z*-**7** could be submitted to the iodination step by ICl. Various reaction conditions have shown that the best chemical yields of **8** were obtained in anhydrous THF at low temperature (de ~ 45%, yield ~ 90%), whereas the diastereoselectivity was maximized in the presence of TBAF (de ~ 85%, yield ~ 50%) or water (de ~ 70%, yield ~ 20%). Under the latter conditions, optically active **1** (ee ~ 30%) was also formed. With *E*-**7** as starting material, the de's were systematically lower. It is interesting to note that similar results were obtained when using pentane-2,4-diol, which is supposed to be a less efficient chiral auxiliary than **5**.[5b,9] However, the main advantage resulting from the use of (3*R*,5*R*)-**5** lied in the possibility to separate the two diastereoisomers (1'*S*)-**8** and (1'*R*)-**8** by flash chromatography, which was not the case for the α-iododioxanes deriving from pentane-2,4-diol. Consequently, a mixture (*Z*/*E* ~ 5.0) of **7** afforded 94% of a separable 32/68 mixture of **8**. The more polar diastereoisomer is also the more abundant. The diastereoisomerically pure dioxanes, which are chemically and configurationally stable at room temperature, were then separately engaged in a two steps hydrolysis procedure[10] leading to (2*S*)- and (2*R*)-**1**, respectively. In contrast, their one-step hydrolysis was difficult and caused considerable racemization.[11] Thus, the 1'-iodo-dioxanes were transacetalized into the corresponding dimethylacetals which are less reluctant to hydrolysis. The transacetalization, carried out in acidic methanol, was completed after 24 h at 50°C. Higher temperatures gave rise to partial racemization. The (2*R*)-2-iodo-dimethylacetal [(2*R*)-**9**] was thus obtained in an 89% yield from (1'*R*)-**8**, whereas (1'*S*)-**8** afforded 87% of (2*S*)-**9**. Moreover, the chiral auxiliary was recovered in an 82% yield. Finally, (2*S*)- and (2*R*)-**1** were smoothly generated by hydrolysis in a two phases system[12] at 0°C for 1h in the dark in an 89% yield.[13] It is worth mentioning that these strongly acidic conditions did not lead to any noticeable racemization of **1** as verified by submitting **1** to prolonged reaction times.[14] Both enantiomers were isolated in a sufficiently pure state by simple extraction of the reaction mixture. Chromatography over silica gel or Florisil induced racemization. **1** may be stored in a dry state at -20°C in the dark and under argon without loss of optical purity.

Two different methods have been developed to determine the enantiomeric excess of **1** after its reduction to 2-iodohexadecanol **10** by $NaBH_4$/MeOH[15] (Scheme 4). Before to apply these methods, the extent of racemization caused by this step has been evaluated (7%) by ^1H NMR after having carried out this reaction in MeOD. It follows that the ee of **1** is slightly underestimated. The ee was measured using the ^1H NMR spectrum of the (*R*)-*O*-methylmandelate esters **11** and **12**[16] (integration of the methine or methoxy protons at 600 MHz), or of the epoxides **13**[17] in the presence of (+)-Eu(hfc)$_3$ (integration of the H-1 *trans* relative to the alkyl chain).[18] Both approaches furnished similar results when applied to optically active **1**, indicating that the extent of racemization during steps ii and iii (scheme 4) is negligible. The LIS method furnished an ee ≥ 93% for (-)-**1** obtained from the less polar (minor) diastereoisomer **8**. The more polar (major) diastereoisomer **8** afforded (+)-**1** having an ee ≥ 89%, based on the optical rotation of (+)-**10**.

The absolute configuration of (-)-**1** has been established as 2*S* by correlation with (2*R*)-(+)-**13** which is a known compound (Scheme 4).[19] This assignment was confirmed by applying Mosher's method to the esters **15** and **16** (Table 1), which are obtained after methanolysis[19] of the epoxide **13** and derivatization of the resulting hydroxyether **14** with (*R*)-*O*-methylmandelic acid.[16] As the less polar α-iododioxane **8**, which is the minor one, afforded (-)-**1**, it was assigned the configuration (1'*S*)-**8**, the major, more polar, diastereoisomer being thus (1'*R*)-**8**.

ester	δH^a	$\Delta\delta=\delta_{15}-\delta_{16}$	δH^b	$\Delta\delta$	δH^c	$\Delta\delta$	Absolute configuration assignment
15	3.30	- 0.13	3.14	- 0.18	1.57	+ 0.13	2*R*
16	3.43		3.32		1.44		2*S*

Table 1. Chemical shifts of the H^a, H^b and H^c protons of both diastereoisomers **15** and **16**.

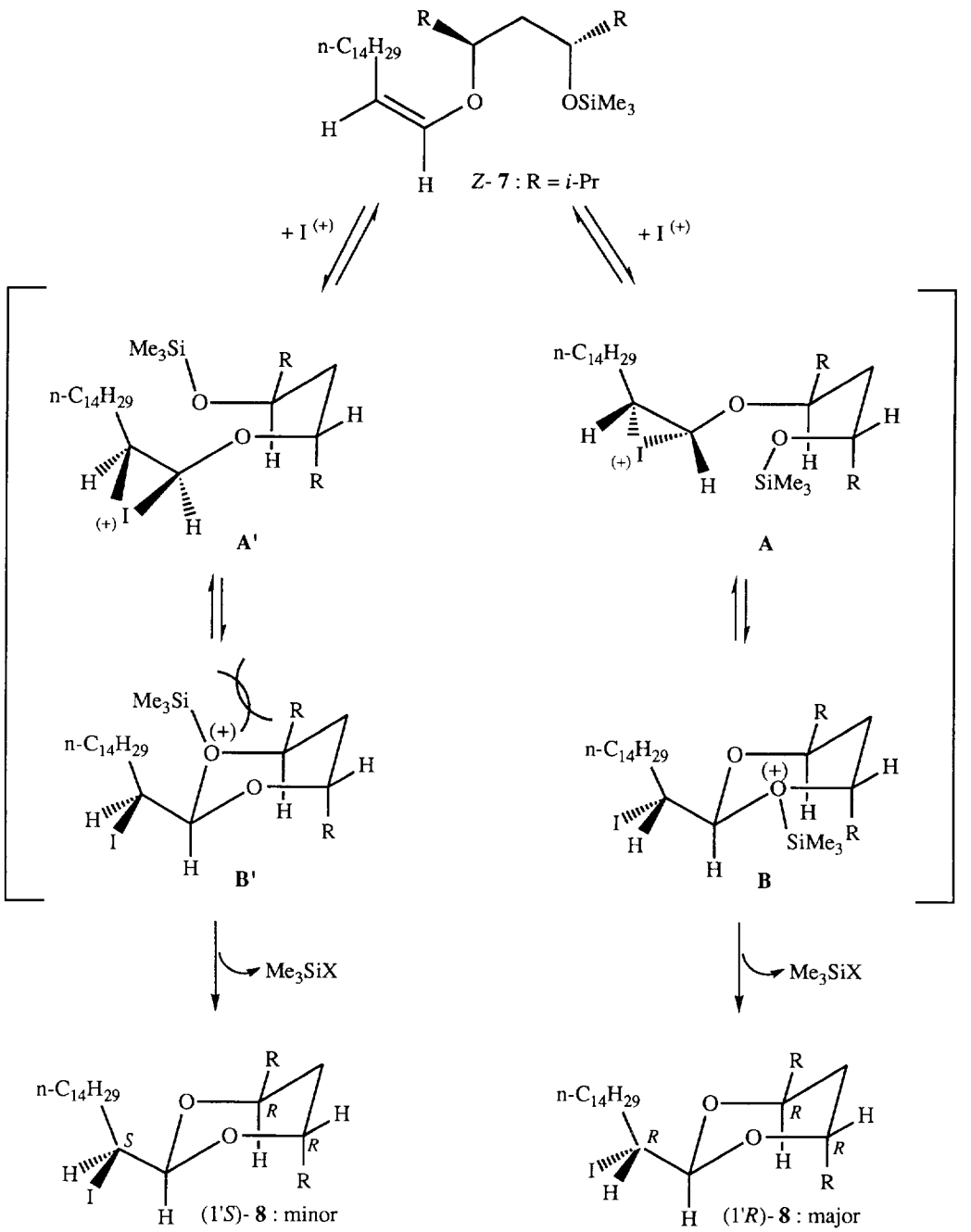


Reagents : i. $NaBH_4$ / MeOH / r.t.; ii. (*R*)-*O*-methylmandelic acid / DCC / DMAP / CH_2Cl_2 / r.t.; iii. MeONa / MeOH / r.t.; iv. MeONa / MeOH / ΔT.

Scheme 4. Enantiomeric excess determination and absolute configuration assignment of (+)- and (-)-**1**.

The stereoselectivity for the iodocyclization of the enol ether *Z*-**7** may be rationalized on the following assumptions (Scheme 5): 1) the reaction is under kinetic control[20]; 2) ICl stereospecifically adds *anti* to the vinyl ether double bond[21]; 3) the iodine addition to the double bond is a reversible and rate undetermining step[22]; 4) the intramolecular attack of the oxygen atom on the intermediate iodonium may be divided into two steps : the first is reversible and slow giving rise to a charged intermediate and the second is reversible or not, depending on the absence or presence of an efficient quencher.[23] In our case, one may consider that intermediate **B** is formed faster because there is no steric repulsion between the trimethylsilyl group and the α methyl group contrary to intermediate **B'**.[24] Thus, in the presence of a good quencher of "Me_3Si^+" (H_2O or TBAF), the last step should be fast and irreversible and (1'*R**,4*R**,6*R**)-**8** formed preferentially.

Having both enantiomers of **1** {(2*R*)-**1**: ee ≥ 89%, (2*S*)-**1**: ee ≥ 93%} at our disposal, their biological properties could be compared, but before doing so their configurational stability to the testing conditions (H_2O_2 production[2a]: KRH buffer at pH 7.4, 37°C, 2h; thyroid adenylyl cyclase[2b]: 50mM TRIS buffer at pH 7.8, 30°C, 1h) had to be assessed. The loss of enantiomeric excess, determined by polarimetry on recovered **1**, was of ±15% and ±40% (mean of two measures) respectively, suggesting that it should be possible to differentiate the biological activities of (2*R*)-**1** and (2*S*)-**1**. The result of the biological testing clearly showed the lack of influence of the absolute configuration of **1** on its biological properties (Table 2).



Scheme 5. Tentative rationalization of the stereochemical outcome for the iodocyclization of *Z*-**7**.

% inhibition at	3 μM	10 μM	30 μM
(±)-**1**	28	57	96
(2*R*)-**1**	38	62	85
(2*S*)-**1**	30	62	81

Table 2. Inhibition of thyroid adenylyl cyclase by **1** (the results represent the mean of triplicates).

We also studied the stereochemical outcome of the biosynthetic path leading to 2-iodoaldehydes. Thus, **1** was generated *in vitro* through lactoperoxidase catalyzed plasmalogen iodination (plasmenylethanolamine / KI / lactoperoxidase / H_2O_2 / phosphate buffer at pH 7.4 / r.t. / 5 min.) (see scheme 1).[1] The subsequent stepwise transformation of the reaction mixture according to scheme 4 (steps i and ii) afforded the (*R*)-*O*-methylmandelate esters **11** and **12** in a 1/1 mixture indicating that natural **1** is racemic. This result is not that much surprising since, for instance, chloroperoxidase has also been shown to unstereoselectively halogenate various substrates.[25]

In conclusion, we have achieved the first asymmetric synthesis of both enantiomers of a 2-iodoaldehyde with ee's ≥ 89% in a five steps procedure and 62% overall yield, through asymmetric iodocyclization of a chiral enantiopure enol ether. This new synthetic scheme is currently under investigation for the preparation of other scalemic 2-heterosubstituted aldehydes such as 2-bromo-, 2-chloro, 2-hydroxy-, 2-amino- and 2-sulfenyl-aldehydes which are valuable 2-functional chirons. Our results also suggest the lack of stereoselectivity in the biosynthesis of 2-iodohexadecanal (**1**) as well as in its interaction with the biological receptors.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a BRUKER WM 250 spectrometer at 250 MHz or, when stated, on a VARIAN UNITY 600 spectrometer at 600 MHz and are reported in ppm from internal TMS on the δ scale. All spectra were recorded in $CDCl_3$, unless otherwise stated. Data are reported as follows: chemical shift [multiplicity (s: singlet, bs: broad singlet, d: doublet, t: triplet, h: heptet, m: multiplet), coupling constants in Hertz, integration]. Ultraviolet spectra were taken on a PHILIPS PU 8720 spectrometer. Infrared spectra were taken with a BRUKER IFS 25 instrument as a film on a NaCl disk. EIMS were recorded on a VG Micromass 7070 spectrometer. Peak intensities are expressed as % relative to the base peak. Optical rotations were measured on a PERKIN-ELMER 141 polarimeter at 589 nm (sodium D line), in a 10 cm cell at 20 °C. Thin layer chromatography analyses were performed on 0.25 mm POLYGRAM silica gel SIL G/UV_{254} precoated plates (MACHEREY-NAGEL). Unless otherwise stated, column chromatographies were performed over silica gel (MERCK 60 0.04-0.063 mm), using the flash technique. During work up, organic solutions were dried over $MgSO_4$.

(4*R*,6*R*)-2-*n*-pentadecyl-4,6-diisopropyl-1,3-dioxane [(4*R*,6*R*)-6]. A mixture containing (3*R*,5*R*)-2,6-dimethylheptane-3,5-diol [(3*R*,5*R*)-**5**][7] (1.090 g, 6.8 mmol), *n*-hexadecanal (prepared by PCC oxidation of *n*-hexadecanol[26]) (1.860 g, 7.7 mmol) and *p*-TsOH (0.022 g, $1.2 \cdot 10^{-4}$ mol) in 7 ml of anhydrous benzene was refluxed with a Dean-Stark trap for 3 h.[24] The cold yellowish solution was then treated with 10 ml of a saturated $NaHCO_3$ solution and the aqueous phase extracted three times with 70 ml portions of ether. The combined organic extracts were washed with a saturated NaCl solution, dried and evaporated *in vacuo*. A silica gel flash chromatography (hexane/AcOEt 98:2 to 5:5) led to the isolation of oily (4*R*,6*R*)-**6** (2.345 g, 90%) and unreacted (3*R*,5*R*)-**5** (0.046 g). (4*R*,6*R*)-**6**: oil. $[\alpha]_D$ -18.2 (c=1.79, $CHCl_3$). EIMS: $C_{25}H_{50}O_2$ (M=382); m/z 381 ($M^{+\bullet}$-H$^\bullet$, 1); 339 ($M^{+\bullet}$-$CHMe_2^\bullet$, 7); 171 ($M^{+\bullet}$-$C_{15}H_{31}^\bullet$, 75); 125 ($C_9H_{17}^+$, 58); 99 (100); 81 (48); 69 (86); 57 (48); 55 (40); 43 (64); 41 (35). IR: 2957, 2923, 2876, 2853, 1470-1435, 1408, 1386, 1367, 1349, 1299, 1261, 1239, 1138, 1117, 1017, 990, 958, 872, 722 cm^{-1}. ^{1}H NMR: 4.68 (t, 5.2 Hz, 1H); 3.48 (ddd, 10.7,

5.6, 1.7 Hz, 1H); 3.34 (ddd, 10.7, 7.1, 3.4 Hz, 1H); 2.26 (dh, 10.7, 6.6 Hz, 1H); 1.77-1.47 (m, 5H); 1.45-1.11 (m, 26H); 0.98 (d, 6.5 Hz, 3H); 0.94 (d, 6.7 Hz, 3H); 0.88 (m, 3H); 0.87 (d, 6.8 Hz, 3H); 0.85 (d, 6.6 Hz, 3H).

(1'*R*,3'*R*)-(1*Z*)- and (1'*R*,3'*R*)-(1*E*)-1-(1'-isopropyl-3'-trimethylsilyloxy-4'-methylpentoxy)-*n*-hexadec-1-ene [*Z*- and *E*-(1'*R*,3'*R*)-7]. To a stirred solution of dioxane (4*R*,6*R*)-**6** (0.332 g, $8.7 \cdot 10^{-4}$ mol) in 1.5 ml of dry CH_2Cl_2 was added *i*-Pr_2NEt (0.484 ml, 2.8 mmol) at room temperature. After cooling to 0°C, 0.503 ml (2.6 mmol) of TMSOTf was added dropwise over 1-2 minutes; the reaction mixture was then allowed to warm to ambient temperature. If the reaction was not completed after stirring for 2 h, the further addition of 0.484 ml of base led to the rapid formation of the enol ethers *Z*- and *E*-(1'*R*,3'*R*)-**7**. Washing of the organic phase with 10 ml of a cold 5% $NaHCO_3$ aqueous solution was followed by 4 extractions with 10 ml portions of pentane. The residue, obtained after evaporation of the solvent *in vacuo*, was purified by flash chromatography on silica gel (hexane/CH_2Cl_2 97:3 + 0.1% Et_3N) to afford, in order of increasing polarity, diastereoisomerically pure *Z*-(1'*R*,3'*R*)-**7** (0.282 g, 71%), a mixture of both isomers (0.032 g, 8%) and pure *E*-(1'*R*,3'*R*)-**7** (0.050 g, 13%). *Z*-(1'*R*,3'*R*)-**7**: oil. $[\alpha]_D$ +27.4 (c=2.19, *n*-hexane). EIMS: $C_{28}H_{58}O_2Si$ (M=454); m/z 454 ($M^{+\bullet}$, 0.7); 439 ($M^{+\bullet}$-Me$^\bullet$, 0.5); 411 ($M^{+\bullet}$-$CHMe_2^\bullet$, 8); 369 (0.9); 321 (2); 312 (4); 297 (3); 223 (2); 215 (7); 171 (5); 145 (45); 125 ($C_9H_{17}^+$, 88); 83 (14); 73 (33); 69 (100); 57 (18); 55 (11); 43 (14); 41(10). IR: 3035, 2960, 2926, 2875, 2855, 1661, 1468, 1386, 1368, 1261, 1251, 1152, 1101, 1081, 1057, 952, 890, 840, 749 cm^{-1}. ^1H NMR: 5.95 (dt, 6.3, 1.4 Hz, 1H); 4.23 (td, 7.3, 6.2 Hz, 1H); 3.69 (ddd, 9.7, 4.2, 2.2 Hz, 1H); 3.52 (ddd, 10.3, 4.6, 2.1 Hz, 1H); 2.11-2.00 (m, 2H); 1.84 (hd, 6.9, 4.6 Hz, 1H); 1.70 (hd, 6.9, 4.2 Hz, 1H); 1.51 (A part of an ABXY system, J_{AB}=14.3, 10.2, 2.4 Hz); 1.39 (B part of an ABXY system, J_{AB}=14.3, 9.8, 2.1 Hz); 1.57-1.17 (AB system + m, 26H); 0.90-0.84 (m, 15H); 0.11 (s, 9H). *E*-(1'*R*,3'*R*)-**7**: oil. $[\alpha]_D$ +20.8 (c=2.48, *n*-hexane). HREIMS: calc. for $C_{28}H_{58}O_2Si$: 454.4206; found: 454.4212; EIMS: m/z 454 ($M^{+\bullet}$, 1); 439 ($M^{+\bullet}$-Me$^\bullet$, 0.5); 411 ($M^{+\bullet}$-$CHMe_2^\bullet$, 10); 369 (1); 321 (3); 312 (5); 297 (4); 223 (2); 222 (2); 215 (9); 171 (9); 145 (45); 125 ($C_9H_{17}^+$, 89); 83 (13); 73 (35); 69 (100); 57 (16); 55 (12); 43 (17); 41(12). IR: 3045, 2959, 2925, 2874, 2854, 1669, 1651, 1467, 1387, 1369, 1261, 1250, 1165, 1133, 1076, 1055, 922, 840, 749 cm^{-1}. ^1H NMR: 6.05 (dt, 12.3, 1.2 Hz, 1H); 4.84 (dt, 12.3, 7.4 Hz, 1H); 3.70 (ddd, 9.9, 4.2, 2.2 Hz, 1H); 3.57 (ddd, 10.2, 4.5, 2.2 Hz, 1H); 1.97-1.82 (m, 3H); 1.69 (hd, 6.9, 4.1 Hz, 1H); 1.47 (A part of an ABXY system, J_{AB}=14.2, 10.3, 2.2 Hz); 1.39 (B part of an ABXY system, J_{AB}=14.2, 10.0, 2.1 Hz); 1.60-1.10 (AB system + m, 26H); 0.90-0.84 (m, 15H); 0.12 (s, 9H).

(1'*S*,4*R*,6*R*)- and (1'*R*,4*R*,6*R*)-2-(1'-iodo-*n*-pentadecyl)-4,6-diisopropyl-1,3-dioxane [(1'*S*)- and (1'*R*)-8]. To a solution of *Z*/*E* -(1'*R*,3'*R*)-**7** (*Z*/*E*~5.0) (0.400 g, $8.8 \cdot 10^{-4}$ mol) in 4.5 ml of dry THF was added dropwise (over a 1-2 minutes period) at -60°C a cold solution of ICl (0.170 g, 1.05 mmol) in THF (1.5 ml). The reaction mixture was stirred for 30 minutes at -60°C, diluted with 15 ml of pentane, washed with 15 ml of 0.1M $Na_2S_2O_3$ and the aqueous phase extracted with 3 further portions of pentane. The organic extracts were evaporated *in vacuo* and the resulting residue submitted to several flash chromatographies on silica gel (hexane/CH_2Cl_2 95:5 to 9:1) affording 0.150 g (34%) of less polar (1'*S*)-**8** (de > 95% by ^1H NMR), 0.022 g (5%) of a mixture of isomers and 0.247 g (55%) of more polar (1'*R*)-**8** (de > 95%). (1'*S*)-**8**: oil. $[\alpha]_D$ -33.8 (c=1.47, *n*-hexane). UV (*n*-hexane): λ_{max} 261 nm, ε=472. HREIMS on the $M^{+\bullet}$-H$^\bullet$ ion: calc. for $C_{25}H_{48}IO_2$: 507.2699; found: 507.2700; EIMS: m/z 507 ($M^{+\bullet}$-H$^\bullet$, 0.3); 493 ($M^{+\bullet}$-Me$^\bullet$, 0.05); 465 ($M^{+\bullet}$-$CHMe_2^\bullet$, 0.8); 381 ($M^{+\bullet}$-I$^\bullet$, 0.08); 368 (0.05); 367 (0.08); 339 (0.07); 338 (0.06); 337 (0.06); 257 (0.2); 239 (0.6); 223 (0.6); 221 (0.3); 197 (0.2); 183 (0.2); 171 ($M^{+\bullet}$-$C_{14}H_{29}CHI^\bullet$, 80); 125 ($C_9H_{17}^+$, 71); 99 (27); 83 (13); 81 (22); 69 (100); 57 (19); 55 (26); 43 (42); 41 (20). IR: 2959, 2925, 2871, 2854, 1468-1432, 1385, 1367, 1298, 1261, 1239, 1146-1014, 981, 957, 870, 722 cm^{-1}. ^1H NMR (C_6D_6): 4.67 (d, 4.5 Hz, 1H); 4.11 (m, 1H); 3.45 (ddd, 10.4, 5.8, 1.9 Hz, 1H); 3.22 (ddd, 11.3, 6.6, 2.7 Hz, 1H); 2.09-1.81 (m, 3H); 1.77-1.50 (m, 2H); 1.48-1.13 (m, 25H); 1.05 (d, 6.5 Hz, 3H); 1.01 (d, 6.7 Hz, 3H); 0.92 (m, 3H); 0.82 (d, 6.8 Hz, 3H); 0.60 (d, 6.6 Hz, 3H). (1'*R*)-**8**: oil. $[\alpha]_D$ -4.2 (c=2.62, *n*-hexane). UV (*n*-hexane): λ_{max} 262 nm, ε=467. EIMS: $C_{25}H_{49}IO_2$ (M=508); m/z 507 ($M^{+\bullet}$-H$^\bullet$, 0.3); 493 ($M^{+\bullet}$-Me$^\bullet$, 0.04); 465 ($M^{+\bullet}$-$CHMe_2^\bullet$, 0.8); 381 ($M^{+\bullet}$-I$^\bullet$, 0.1);

368 (0.1); 367 (0.1); 339 (0.2); 257 (0.3); 239 (0.6); 223 (0.6); 197 (0.3); 183 (0.2); 171 ($M^{+\bullet}$-$C_{14}H_{29}CHI^{\bullet}$, 76); 125 ($C_9H_{17}^+$, 79); 99 (29); 83 (15); 81 (22); 69 (100); 57 (21); 55 (20); 43 (32); 41 (15). IR: 2959, 2925, 2871, 2854, 1468-1432, 1385, 1367, 1299, 1261, 1239, 1141, 1108, 1092, 1023, 986, 870, 721 cm^{-1}. ^1H NMR (C_6D_6): 4.54 (d, 4.4 Hz, 1H); 4.11 (ddd, 9.0, 4.5 Hz, 1H); 3.45 (ddd, 10.5, 5.9, 2.0 Hz, 1H); 3.23 (ddd, 11.4, 6.5, 2.7 Hz, 1H); 2.08-1.83 (m, 3H); 1.77-1.52 (m, 2H); 1.49-1.14 (m, 25H); 1.06 (d, 6.5 Hz, 3H); 0.99 (d, 6.7 Hz, 3H); 0.92 (m, 3H); 0.82 (d, 6.8 Hz, 3H); 0.61 (d, 6.6 Hz, 3H).

(2*S*)-1,1-dimethoxy-2-iodo-*n*-hexadecane [(2*S*)-9] and its enantiomer (2*R*)-9. (1'*S*)-**8** (102 mg, $2.0 \cdot 10^{-4}$ mol) was heated at 50°C (oil bath) in the presence of *p*-TsOH (304 mg, 1.6 mmol) in 16 ml of MeOH. The reaction mixture was stirred for 23 h, after which it was reduced *in vacuo* to 10 ml, diluted with 10 ml of water, neutralized with a saturated $NaHCO_3$ aqueous solution and extracted four times with 25 ml of pentane. Evaporation of the organic phase *in vacuo* led to a (2*S*)-**9**-enriched residue while the aqueous layer afforded, after evaporation of MeOH, dilution with 10 ml of water and extraction three times with 20 ml of AcOEt, a (3*R*,5*R*)-**5**-enriched residue. A flash chromatography (hexane/CH_2Cl_2 98:2 to 9:1, then hexane/AcOEt 7:3) of the combined residues gave 5 mg of unreacted (1'*S*)-**8** (de~95%), (2*S*)-**9** (72 mg, 87%) as a colourless oil and 27.4 mg of (3*R*,5*R*)-**5** (85%). (2*S*)-(-)-**9**: oil. $[\alpha]_D$ -15.7 (c=3.15, *n*-hexane). UV (*n*-hexane): λ_{max} 261 nm, ε=463. HREIMS on the $M^{+\bullet}$-$H^{\bullet}$ ion: calc. for $C_{18}H_{36}IO_2$: 411.1760; found: 411.1763; EIMS: m/z 411 ($M^{+\bullet}$-$H^{\bullet}$, 0.04); 381 ($M^{+\bullet}$-$MeO^{\bullet}$, 0.7); 285 ($M^{+\bullet}$-$I^{\bullet}$, 3); 253 ($M^{+\bullet}$-$I^{\bullet}$-MeOH, 0.7); 198 (1); 156 (1); 75 ($CH(OMe)_2^+$, 100); 71 (9); 57 (5); 55 (6); 43 (9); 41(9). IR: 2954, 2925, 2854, 1464-1456, 1377, 1349, 1189, 1114, 1073, 1056, 958, 722 cm^{-1}. ^1H NMR: 4.26 (d, 5.6 Hz, 1H); 4.12-4.04 (m, 1H); 3.43/3.42 (2s, 6H), 1.84-1.70 (m, 2H); 1.42-1.17 (m, 24H); 0.88 (m, 3H).

The same procedure was applied to (1'*R*)-**8** affording 89% of (2*R*)-**9** and 78% of (3*R*,5*R*)-**5**. (2*R*)-(+)-**9**: $[\alpha]_D$ +15.6 (c=4.36, *n*-hexane). Same spectral properties as (2*S*)-(-)-**9**.

(2*S*)-2-iodo-*n*-hexadecanal [(2*S*)-1] and its enantiomer (2*R*)-1. A heterogenous mixture containing (2*S*)-**9** (40 mg, $9.7 \cdot 10^{-5}$ mol) dissolved in 540 µl of CH_2Cl_2 and 270 µl of 70% aqueous CF_3CO_2H was stirred at 0°C in the dark for 1 h. After addition of 10 ml of cold water and extraction with 10 ml of pentane, the aqueous phase was neutralized by aqueous $NaHCO_3$ and extracted three times with pentane. The organic extracts were evaporated *in vacuo* to furnish crude {contaminated by ~8% of unreacted (2*S*)-**9**} (2*S*)-**1** (34.3 mg, ~88%) as a white solid. This material was used without further purification for the biological testing and for its enantiomeric excess determination. (2*S*)-(-)-**1**: $[\alpha]_D$ -97 (c=0.80, *n*-hexane, ee ≥ 93%). UV (*n*-hexane): λ_{max} 276 nm, ε=457. HREIMS: calc. for $C_{16}H_{31}IO$: 366.1420; found: 366.1421; EIMS: m/z 366 ($M^{+\bullet}$, 0.4); 239 ($M^{+\bullet}$-$I^{\bullet}$, 19); 221 ($M^{+\bullet}$-$I^{\bullet}$-H_2O, 12); 170 ($CHICHOH^{+\bullet}$, 14); 137 (14); 123 (27); 109 (51); 95 (86); 83 (75); 81 (71); 69 (76); 57 (98); 55 (87); 43 (100); 41(81). IR: 2924, 2852, 2720, 1720, 1464, 1374, 1260, 1088, 800, 722 cm^{-1}. ^1H NMR: 9.26 (d, 3.2 Hz, 1H); 4.45 (td, 7.3, 3.2 Hz, 1H); 2.05-1.82 (m, 2H); 1.57-1.12 (m, 24H); 0.88 (m, 3H).

Similarly, crude (2*R*)-**1** contaminated by ~7% of unreacted starting material was obtained from (2*R*)-**9** in a ~90% yield. (2*R*)-(+)-**1**: $[\alpha]_D$ +94 (c=0.90, *n*-hexane, ee ≥ 89%). Same spectral properties as (2*S*)-(-)-**1**.

(2*S*)-2-iodo-*n*-hexadecan-1-ol [(2*S*)-10] and its enantiomer (2*R*)-10. $NaBH_4$ (2.1 mg, $5.6 \cdot 10^{-5}$ mol) was added all at once to a stirred solution of (2*S*)-**1** (20.0 mg, $5.5 \cdot 10^{-5}$ mol) in 1 ml of MeOH kept in the dark and at room temperature. After 30 minutes, the reaction mixture was quenched with 10 ml of water and extracted four times with 10 ml of pentane. Evaporation of the organic solvent and flash chromatography on silica gel (hexane/CH_2Cl_2 8:2 to 7:3) gave (2*S*)-**10** (13.1 mg, 65%). (2*S*)-(-)-**10**: oil. $[\alpha]_D$ -30.5 (c=2.03, *n*-hexane, ee ≥ 93%). UV (*n*-hexane): λ_{max} 257 nm, ε=536. HREIMS on the $M^{+\bullet}$-$OH^{\bullet}$ ion: calc. for $C_{16}H_{32}I$: 351.1549; found: 351.1542; EIMS: m/z 351 ($M^{+\bullet}$-$OH^{\bullet}$, 0.2); 269 (1); 241 ($M^{+\bullet}$-$I^{\bullet}$, 19); 167 (2); 153 (3); 139 (6); 125 (21); 111 (46); 97 (87); 83 (96); 69 (100); 57 (83); 55 (87); 43 (69); 41(50). IR: 3362, 2922, 2852, 1464, 1376, 1262, 1158, 1096-1018, 802, 722, 608 cm^{-1}. ^1H NMR: 4.28-4.18 (m, 1H); 3.79-3.62 (m, 2H); 1.94-1.70 (m, 3H); 1.63-1.10 (m, 24H); 0.88 (m, 3H).

By the same procedure, (2*R*)-**10** was obtained from (2*R*)-**1** and had spectral properties identical to those of its enantiomer. (2*R*)-(+)-**10**: $[\alpha]_D$ +29.1 (c=1.63, *n*-hexane, ee ≥ 89%).

(*R*)-*O*-methylmandelate esters (2*S*)-11 and (2*R*)-12. Racemic 2-iodohexadecanol (±)-**10** (12.5 mg, $3.4 \cdot 10^{-5}$ mol) was derivatized according to the procedure of Trost *et al.*[16] using DMAP (0.3 mg, $2.5 \cdot 10^{-6}$ mol), (*R*)-*O*-methylmandelic acid (8.5 mg, $5.1 \cdot 10^{-5}$ mol) and DCC (10.5 mg, $5.1 \cdot 10^{-5}$ mol). Thus, the latter (dissolved in 0.4 ml of CH_2Cl_2) was added under stirring to a 0.3 ml solution of the other reagents in dry CH_2Cl_2. The reaction was allowed to proceed at room temperature for 1 h, the medium was then filtered, evaporated *in vacuo* and purified by flash chromatography on silica gel (hexane/CH_2Cl_2 7:3) affording a 1/1 mixture of the two esters **11** and **12** (15.1 mg, 86%), that could not be separated under these conditions. (2*S*)-**11** + (2*R*)-**12**: oil. UV (*n*-hexane): λ_{max} 204 nm, ε=8303; 259 nm, ε=679. EIMS: $C_{25}H_{41}IO_3$ (M=516); m/z 516 ($M^{+\bullet}$, 0.6); 389 ($M^{+\bullet}$-I$^\bullet$, 2); 368 (1); 351 ($M^{+\bullet}$-MeOCHC$_6$H$_5$CO$_2^\bullet$, 2); 236 (1); 211 (1); 197 (2); 183 (3); 169 (3); 167 (4); 155 (5); 121 (MeOCHC$_6$H$_5^+$, 100); 91 (50); 69 (37); 57 (41); 55 (49); 43 (53); 41 (53). IR: 3029, 2924, 2854, 1756, 1464, 1456, 1260, 1246, 1198, 1166, 1116, 1004, 798, 728, 696 cm^{-1}. ^{1}H NMR-600 MHz (C_6D_6): 7.73-7.00 (m, 10H); 4.78 (**11**)/4.77 (**12**) (2s, 2H); 4.27 (**12**) (dd, 11.8, 5.9 Hz, 1H); 4.25 (**11**) (dd, 11.6, 6.5 Hz, 1H); 4.11 (**11**) (dd, 11.4, 6.6 Hz, 1H); 4.08 (**12**) (dd, 11.8, 6.3 Hz, 1H); 3.86-3.80 (m, 2H); 3.29 (**11**)/3.29 (**12**) (2s, 6H); 1.45-0.77 (m, 58H).

(2*R*)-1,2-epoxy-*n*-hexadecane [(2*R*)-13]. To a solution of (2*S*)-**10** (20 mg, $5.4 \cdot 10^{-5}$ mol, ee≥93%) in 400 µl of MeOH was added a freshly prepared solution of MeONa (2 eq.) in 100 µl of MeOH and stirring was maintained for 1 h at room temperature. The reaction mixture was diluted with 10 ml of water and extracted four times with 10 ml of pentane. Evaporation of the organic extracts *in vacuo* followed by flash chromatography on silica gel (hexane/CH_2Cl_2 8:2) led to (2*R*)-**13** (11.0 mg, 84%). (2*R*)-(+)-**13**: oil. $[\alpha]_D$ +10.2 (c=1.76, *n*-hexane, ee ≥ 93%); lit.[19]: $[\alpha]_D$ +9.64 (c=3.64, *n*-hexane, ee=100%). EIMS: $C_{16}H_{32}O$ (M=240); m/z 241 ($M^{+\bullet}$+H$^\bullet$, 0.2); 240 ($M^{+\bullet}$, 0.3); 239 ($M^{+\bullet}$-H$^\bullet$, 0.2); 222 ($M^{+\bullet}$-H_2O, 0.4); 208 (0.8); 194 (1); 182 (2); 180 (2); 166 (2); 152 (3); 137 (4); 123 (9); 109 (20); 96 (52); 82 (80); 71 (83); 57 (60); 55 (89); 43 (96); 41(100). IR: 3042, 2926, 2854, 1466, 1410, 1376, 1260, 1098, 1022, 916, 836, 808, 722 cm^{-1}. ^{1}H NMR (C_6D_6): 2.66-2.55 (m, 1H); 2.37 (dd, 5.3, 3.9 Hz, 1H); 2.11 (dd, 5.3, 2.6 Hz, 1H); 1.46-1.15 (m, 26H); 0.91 (m, 3H).

(±)-1-methoxy-*n*-hexadecan-2-ol [(±)-14]. Oxirane (±)-**13** (10 mg, $4.2 \cdot 10^{-5}$ mol) was methanolyzed in 500 µl of MeOH in the presence of 0.1 eq. of freshly prepared MeONa at reflux. After ~7 h, the reaction mixture was evaporated *in vacuo* and the residue purified by flash chromatography on silica gel (hexane/ether 8:2) to afford (±)-**14** (9.4 mg, 83%). (±)-**14**: oil. EIMS: $C_{17}H_{36}O_2$ (M=272); m/z 255 ($M^{+\bullet}$-OH$^\bullet$, 6); 227 ($M^{+\bullet}$-CH$_2$OMe$^\bullet$, 67); 213 (10); 208 (18); 139 (12); 125 (29); 111 (52); 97 (93); 83 (100); 71 (47); 69 (92); 57 (78); 55 (73); 47 (46); 45 (38); 43 (63); 41(43). IR: 3440, 2922, 2873, 2854, 1472-1462, 1377, 1195, 1118-1103, 968, 948, 722 cm^{-1}. ^{1}H NMR: 3.76-3.63 (m, 1H); 3.33 (A part of an ABM system, J_{AB}=9.4, 3.0 Hz, 1H); 3.32 (s, 3H); 3.16 (B part of an ABM system, J_{AB}=9.4, 8.0 Hz, 1H); 2.16 (d, 3.3 Hz, 1H); 1.45-1.11 (m, 26H); 0.88 (m, 3H).

(*R*)-*O*-methylmandelate esters (2*R*)-15 and (2*S*)-16. Both diastereoisomers **15** and **16** were prepared from racemic or enantiomerically enriched **14** in an analogous manner to the one reported hereabove for the synthesis of the (*R*)-*O*-methylmandelate esters **11** and **12**. Thus, a flash chromatography on silica gel (hexane/ether 9:1) afforded, in order of increasing polarity, the easily separable epimers **15** and **16** in a 79% yield. (2*R*)-**15**: oil. UV (*n*-hexane): λ_{max} 205 nm, ε=8706; 258 nm, ε=234. HREIMS: calc. for $C_{26}H_{44}O_4$ 420.3239; found: 420.3237; EIMS: m/z 420 ($M^{+\bullet}$, 0.3); 344 (0.2); 255 ($M^{+\bullet}$-MeOCHC$_6$H$_5$CO$_2^\bullet$, 0.7); 222 (0.2); 148 (0.7); 121 (MeOCHC$_6$H$_5^+$, 100); 105 (2); 97 (1); 91 (3); 83 (2); 77 (4); 71 (2); 69 (3); 57 (3); 55 (4); 45 (5); 43 (5); 41 (4). IR: 3090, 3068, 3032, 2926, 2854, 1750, 1732, 1464, 1456, 1256, 1200, 1176, 1118, 998, 726, 698 cm^{-1}. ^{1}H NMR: 7.53-7.29 (m, 5H); 5.06 (m, 1H); 4.78 (s, 1H); 3.44 (s, 3H); 3.36-3.24 (m, 2H); 3.14 (s, 3H); 1.64-1.49 (m, 2H); 1.39-1.13 (m, 24H); 0.88 (m, 3H). (2*S*)-**16**: oil. UV (*n*-hexane): λ_{max}

206 nm, ε=8330. EIMS and IR identical to those of **15**. ^{1}H NMR: 7.50-7.29 (m, 5H); 5.04 (m, 1H); 4.78 (s, 1H); 3.48-3.37 (m, 2H); 3.42 (s, 3H); 3.32 (s, 3H); 1.48-1.40 (m, 2H); 1.38-0.80 (m, 27H).

ACKNOWLEDGEMENTS

One of us (C.J.) gratefully acknowledges the Ministry of Education (Luxemburg), the Rotary Club (Luxembourg), the Fondation Mathieu (Luxemburg) and NATO for the award of a fellowship. We thank V. Panneels for the biological testing, Dr R. Ottinger and Mr C. Maerschalk for the NMR spectra as well as Dr M. Kaisin and Mr C. Moulard for the mass spectra.

REFERENCES AND NOTES

1. Pereira, A.; Braekman, J.C.; Dumont, J.E.; and Boeynaems, J.M. *J. Biol. Chem.* **1990**, *265* (28), 17018-17025.
2. a) Panneels, V.; Van den Bergen, H.; Jacoby, C.; Braekman, J.C.; Van Sande, J.; Dumont, J.E.; and Boeynaems, J.M. *Mol. Cell. Endocrinol.* **1994**, *102*, 167-176. b) Panneels, V.; Van Sande, J.; Van den Bergen, H.; Jacoby, C.; Braekman, J.C.; Dumont, J.E.; and Boeynaems, J.M. *Mol. Cell. Endocrinol.* **1994**, *106*, 41-50.
3. a) Martin, V.S.; and Palazon, J.M. *Tetrahedron Lett.* **1992**, *33*, 2399-2402. b) Castaldi, G.; Giordano, C.; and Restelli, A. *Chemical Abstracts* **1988**, *108*, P 37820s.
4. Alexakis, A.; and Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477-511.
5. a) Naruse, Y.; and Yamamoto, H. *Tetrahedron* **1988**, *44*, 6021-6029. b) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; and Tai, A. *Tetrahedron* **1990**, *46*, 5955-5966.
6. a) Gassman, P.G.; and Burns, S.J. *J. Org. Chem.* **1988**, *53*, 5574-5576. b) Gassman, P.G.; Burns, S.J.; and Pfister, K.B. *J. Org. Chem.* **1993**, *58*, 1449-1457.
7. Jacoby, C.; Braekman, J.C.; and Daloze, D. *Tetrahedron : Asymmetry* **1995**, *6*, 753-756.
8. For other examples of chiral enol ether formation by acetal opening see ref. 5, 9 and: a) Fioravanti, S.; Loreto, M.A.; Pellacani, L.; and Tardella, P.A. *Tetrahedron* **1991**, *47*, 5877-5882. b) Tang, S.; and Kennedy, R.M. *Tetrahedron Lett.* **1992**, *33*, 7823-7826.
9. a) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; and Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807-3810. b) Sugimura, T.; Nishiyama, N.; Tai, A.; and Hakushi, T. *Tetrahedron : Asymmetry* **1993**, *4*, 43-44. c) Sugimura, T.; Katagiri, T.; and Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367-368.
10. a) Stowell, J.C.; and Polito, M.A. *J. Org. Chem.* **1992**, *57*, 4560-4562. b) Stowell, J.C.; and Keith, D.R. *Synthesis* **1979**, 132-133.
11. Sammakia, T.; and Berliner, M.A. *J. Org. Chem.* **1994**, *59*, 6890-6891.
12. Ellison, R.A.; Lukenbach, E.R.; and Chiu, C.W. *Tetrahedron Lett.* **1975**, 499-502.
13. For recently published deprotection conditions of α-haloaldehyde dimethylacetals see : a) Boni, M.; Ghelfi, F.; Pagnoni, U.M.; and Pinetti, A. *Synth. Commun.* **1993**, *23*, 1915-1921. b) Benincasa, M.; Boni, M.; Ghelfi, F.; and Pagnoni, U.M. *Synth. Commun.* **1995**, *25*, 1843-1848.
14. This result is in agreement with those already reported, see: Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; and Kremer, K.A.M. *Tetrahedron* **1984**, *40*, 1345-1359.
15. De Kimpe, N.; and Verhé, R. *"The chemistry of α-haloketones, α-haloaldehydes and α-haloimines"* edited by Patai, S. and Rappoport, Z., John Wiley & Sons, Chichester, **1988**, p. 435.
16. Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; and Springer, J.P. *J. Org. Chem.* **1986**, *51*, 2370-2374.
17. Oppolzer, W.; and Dudfield, P. *Tetrahedron Lett.* **1985**, *26*, 5037-5040.
18. a) Groves, J.T.; and Myers, R.S. *J. Am. Chem. Soc.* **1983**, *105*, 5791-5796. b) Simon, E.S.; Whitesides, G.M.; Cameron, D.C.; Weitz, D.J.; and Cooney, C.L. *J. Org. Chem.* **1987**, *52*, 4042-4044.
19. Ohta, H.; and Tetsukawa, H. *J. Chem. Soc., Chem. Commun.* **1978**, 849-850.

20. a) Castaldi, G.; Cavicchioli, S.; Giordano, C.; and Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018-3027. b) Giordano, C.; Coppi, L.; and Restelli, A. *J. Org. Chem.* **1990**, *55*, 5400-5402. c) Giordano, C.; and Coppi, L. *J. Org. Chem.* **1992**, *57*, 2765-2766.
21. Dana, G.; Convert, O.; and Perrin, C. *J. Org. Chem.* **1975**, *40*, 2133-2135.
22. Horton, D.; Priebe, W.; and Sznaidman, M. *Carbohydr. Res.* **1990**, *205*, 71-86.
23. Yamamoto, K.; Shimizu, M.; Yamada, S.; Iwata, S.; and Hoshino, O. *J. Org. Chem.* **1992**, *57*, 33-39.
24. Denmark, S.E.; and Almstead, N.G. *J. Am. Chem. Soc.* **1991**, *113*, 8089-8110.
25. Ramakrishnan, K.; Oppenhuizen, M.E.; Saunders, S.; and Fisher, J. *Biochemistry* **1983**, *22*, 3271-3277.
26. Corey, E.J.; and Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647-2650.

(*Received in Belgium* 27 *February* 1996; *accepted* 21 *June* 1996)