Tetrahedron Letters 52 (2011) 3447–3450

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthetic studies toward the cytotoxic norditerpene (+)-harringtonolide: setting up key-stereogenic centers of the cyclohexane ring D

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ARTICLE INFO

Article history:
Received 28 February 2011
Revised 19 April 2011
Accepted 26 April 2011
Available online 5 May 2011

Keywords:
Total synthesis
Intramolecular Diels–Alder reactions
Pseudosymmetry
Lactone contraction
Epoxidation

ABSTRACT

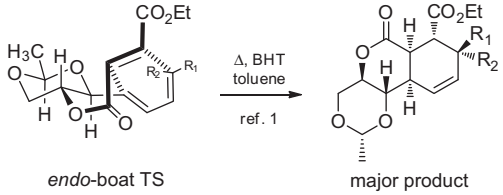
The pivotal stereogenic centers of the asymmetric cycle D of (+)-harringtonolide were installed by functionalization of an enantiomerically pure IMDA cycloadduct, constructed from the chiral pool. The chiral 1,3-dioxane template used to direct the IMDA reaction was unraveled in an acidic medium, through spectacular hydrolysis of the acetal and concomitant lactone ring contraction. The central cyclohexene was selectively epoxidized either on the β- or on the α-side depending on the substitution pattern. The reactivity of several epoxide intermediates was challenged toward the construction of the oxygenated bridges of harringtonolide. We found one of them suitable for an access to another natural product, tetrodecamycin, which shares a similar substitution pattern as harringtonolide. Alternatively, functionalization led to set up key-stereocenters, en route to the asymmetric total synthesis of harringtonolide. The reactivity of the epoxide intermediates gave helpful insight for future work on this total synthesis.

We recently reported a detailed study on the synthesis of naturally occurring cyclohexene rings using stereodirected intramolecular Diels–Alder (IMDA) reactions through asymmetric 1,3-dioxane tethering.[1] The method is particularly attractive in the sense that it allows cycloaddition of a (*E*,*Z*)-diene and a fumarate dienophile with high diasteroselectivities, through a chiral 1,3,9-decatrienoate system. It has been used for the preparation of important chiral intermediates in the total synthesis of natural products, a work that is underway in our laboratory (Scheme 1).

We now report the functionalization of an important cycloadduct arising from the IMDA reaction of a (*E*,*Z*)-diene substrate (R_1 = H, R_2 = Me) toward the total synthesis of natural products in the norditerpene series. Indeed, such a chiral cyclohexene intermediate can be predicted when looking at cycle D of the title compound harringtonolide (1), isolated from the plum yew *Cephalotaxus harringtonia*,[2] and of the parent hainanolidol **2** (Fig. 1).[3] Compound 1 is strongly cytotoxic with a half inhibitory concentration (IC_{50}) of 43 nM.[4] It is also phytotoxic,[2] which probably reflects an important defensive function for the plant in nature. This compound holds a central and highly substituted cyclohexane ring (cycle D) which bears most of the asymmetric centers of the natural product.

Few studies have been reported toward the total syntheses of **1** and **2**, and none of them were undertaken in the asymmetric series. The conversion of **2** into **1** was early reported, using lead tetraacetate oxidation.[5] Later, Mander and co-workers reported the racemic total synthesis of **2** (a formal synthesis of **1**).[6] In their synthesis, cycle D was installed from an advanced intermediate using an aldol reaction. An elegant second generation strategy was then reported by Mander and Sullivan in 2003, constructing the racemic cycle D by an intermolecular Diels–Alder reaction between an indenone dienophile and an α-pyrone diene.[7] More recently, our contribution on the IMDA reaction using substrates derived from the chiral pool provided a novel asymmetric entry toward the chiral cycle D of the *Cephalotaxus* norditerpene series. Herein, we report our work and observations on the functionalization of this pivotal ring.[1,8]

The Diels–Alder substrate **3**, bearing a stereodirecting 1,3-dioxane, was made in 9 steps from D-glucose according to our previous reports.[1] The thermal IMDA cycloaddition of **3** in toluene and in the



Scheme 1. The chiral 1,3-dioxane templated IMDA reaction.

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doi:10.1016/j.tetlet.2011.04.101

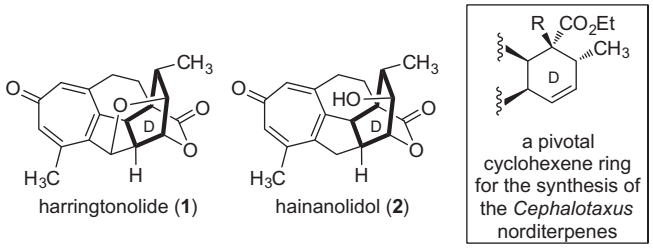
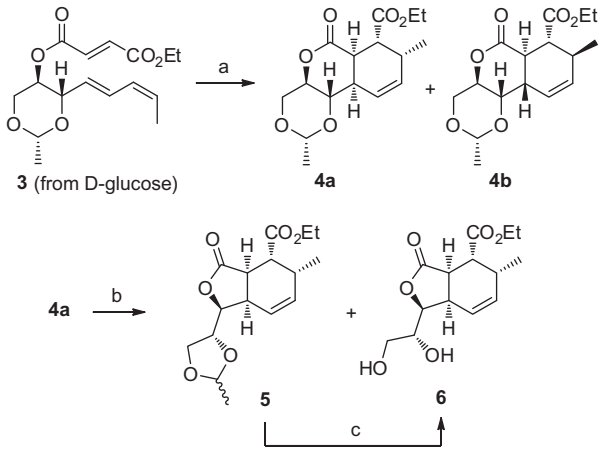
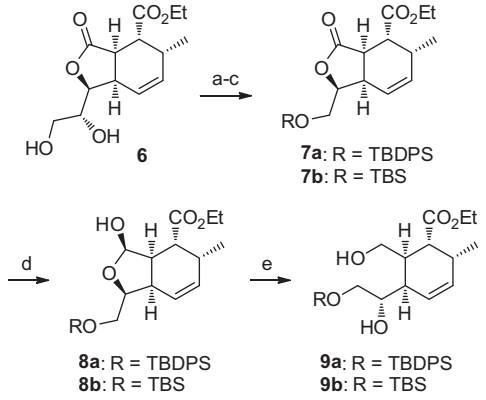


Figure 1. The *Cephalotaxus* norditerpenes (**1** and **2**) and structure of a possible synthetic intermediate toward the ring D.

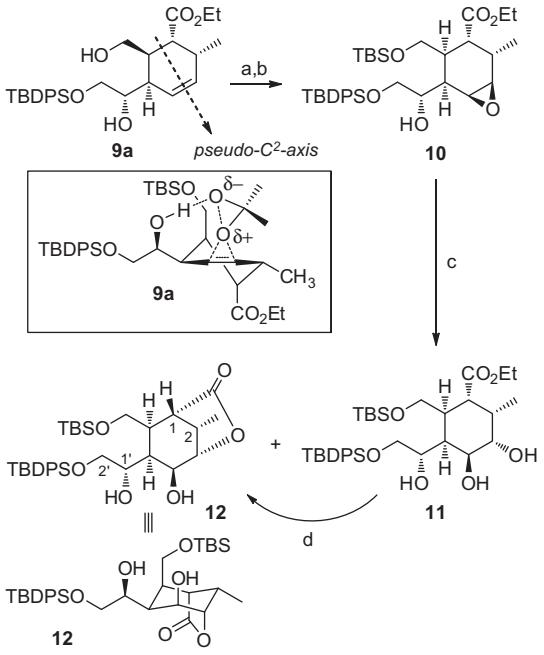


Scheme 2. Asymmetric synthesis of the pivotal cyclohexene ring D of harringtonolide (**1**). Reagents and Conditions: (a) BHT (0.2 equiv), toluene, 225 °C (sealed tube), 85 h (**4a**: 66%; **4b**: 21%); (b) TFA/H_2O (1:1), 80 °C (**5**: 17%, α:β = 3:1; **6**: 67%); (c) 1 M aq HCl, acetone (1:1), rt (85%).

presence of BHT (0.2 equiv) afforded the *endo* cycloadduct **4a** in 66% yields (Scheme 2). It was accompanied with 21% of the *exo* isomer **4b** (3:1 stereoisomeric ratio). Despite the (*E*,*Z*) geometry of **3**, this reaction was particularly efficient and was performed on a five gram-scale. Then, unraveling of the dioxane moiety of **4a** was undertaken by an acidic treatment in TFA/H_2O at 80 °C, leading to acetal hydrolysis and concomitant contraction of the lactone ring. In fact diol **6** was obtained in 67% yields, along with a 3:1 α/β-mixture of dioxolane **5** in 17% yields. Compound **5** was recycled by hydrolytic treatment in aqueous HCl–acetone to recover **6** in 85% yield.



Scheme 3. Synthesis of diols **9a** and **9b**. Reagents and Conditions: (a) $NaIO_4$, MeOH, H_2O, rt; (b) $NaBH_4$, MeOH, 0 °C, rt; (c) TBDPSCl (**7a**) or TBSCl (**7b**), imidazole, DMAP, CH_2Cl_2 (overall yields: **7a**: 98%; **7b**: 72%); (d) L-Selectride, THF, −78 °C (**8a**: 75%; **8b**: 99%); (e) $NaBH_4$, MeOH (**9a**: 87%; **9b**: 95%).



Scheme 4. Effect of the β-hydroxyl group on the epoxidation outcome of the pseudosymmetric cyclohexene **9a**. Reagents and Conditions: (a) TBSCl, imidazole, DMAP, CH_2Cl_2 (50%); (b) DMDO, CH_2Cl_2 (100%); (c) PTSA·H_2O, toluene, 80 °C, 2 h (**11**: 46%, **12**: 25%); (d) PTSA·H_2O, toluene, 80 °C, 1.5 h (70%).

Diol **6** was cleaved in the presence of sodium periodate before reduction and silyl-protection of the resulting primary alcohol (Scheme 3), affording bicyclic compounds **7a** and **7b** in 98% and 72% yields, respectively, over the three steps. L-Selectride® reduction of the lactone provided the corresponding lactols **8a** and **8b** in 75% and 99% yields. Unfortunately, attempts for Wittig methylenation of the lactols only resulted in unwanted reactions or degradation. Instead, conversion into the corresponding diols **9a** and **9b** was undertaken in the presence of $NaBH_4$ in MeOH, giving the expected products in 87% and 95% yields, respectively.

After selective silylation of the primary alcohol of diol **9a**, the quantitative epoxidation of the cyclohexene ring in the presence of DMDO[9] provided β-epoxide **10** with complete stereocontrol (Scheme 4). Since the cyclohexene ring holds a pseudo-C^2-symmetry axis, we were first particularly puzzled by the outcome of the epoxidation on such a system. The presence of two bulky silyl protecting groups on the β-face was expected to direct the epoxidation on the α-face. Yet the remaining alcohol had a much more important effect on this reaction, leading to complete β-selectivity, presumably through hydrogen bonding of DMDO (box in Scheme 4).[10] Indeed, when the secondary alcohol of **9a** was acetylated, the epoxidation was not stereoselective under the same conditions (α/β = 1:1), which was consistent with pseudo-symmetry of both faces. Eventually, when treating β-epoxide **10** with PTSA in wet toluene, diol **11** was obtained. Final transannular cyclization of the

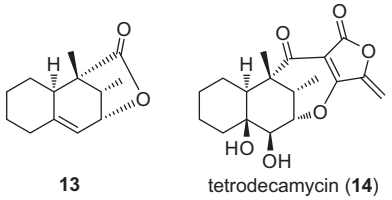
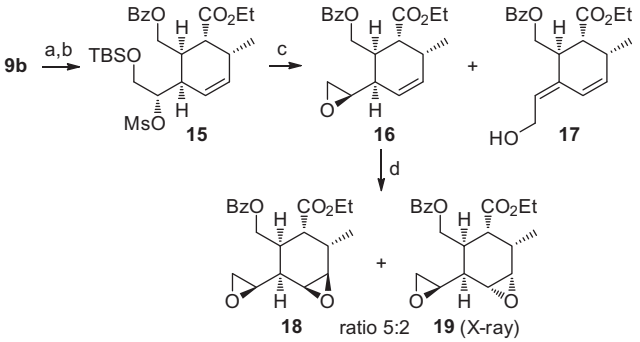


Figure 2. Structure of tetrodecamycin (**14**) and of Paintner's intermediate (**13**) toward **14**.



Scheme 5. Synthesis of the epoxide **16**, bearing the key-stereogenic center of harringtonolide. Reagents and Conditions: (a) BzCl, pyridine, CH_2Cl_2, reflux (75%); (b) MsCl, pyridine, CH_2Cl_2, reflux (93%); (c) TBAF, CH_2Cl_2, rt (**16**: 81%; **17**: 10%); (d) DMDO, CH_2Cl_2, acetone, 0 °C then rt (100%, β:α = 5:2) or mCPBA, $NaHCO_3$, CH_2Cl_2, rt (90%, β:α = 5:2).

α-hydroxyl with the ester furnished the bridged lactone **12**, whose structure was determined by 2D NMR.[11] Although the lactone bridge in **12** was not correctly positioned compared to harringtonolide **1**, we found it very close to the one made by Paintner et al. (**13**)[12] for their synthesis of tetrodecamycin (**14**),[13] sharing similar substitution pattern as our target compound (Fig. 2).

Alternatively, esterification of the primary alcohol of **9b** and mesylation of the secondary one provided intermediate **15** in 70% yields (Scheme 5). The homoallylic epoxide **16** was obtained in 83% yield through deprotection of the TBS group and subsequent mesylate substitution with inversion of configuration as required, with regard to the stereochemistry of **1**.[14] Product **16** was accompanied by 10% of dienol **17** when the reaction was performed in CH_2Cl_2, while greater amounts of this undesired product were observed in THF (up to 40%).

Remarkably, compound **16** holds most of the key-stereogenic centers of harringtonolide (**1**). Therefore, functionalization of this intermediate may provide interesting intermediates for the asymmetric synthesis of *Cephalotaxus* norditerpenes. We found that DMDO epoxidation of **16** afforded a 5:2 mixture of stereoisomers in favor of the β-epoxide **18**. Similar results were obtained using mCPBA in the presence of $NaHCO_3$. However, in these cases, since no hydroxyl group can direct the epoxidation (as for **9a**), we suggest that this selectivity may arise from higher steric hindrance

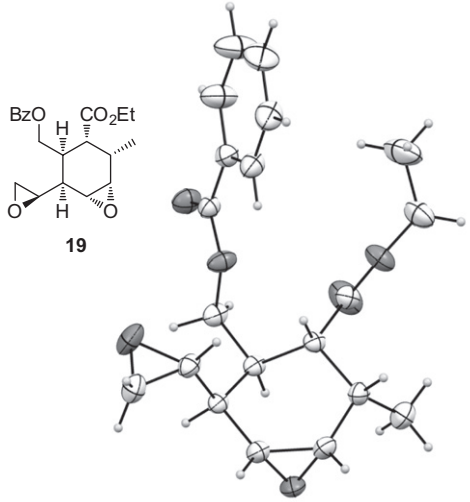
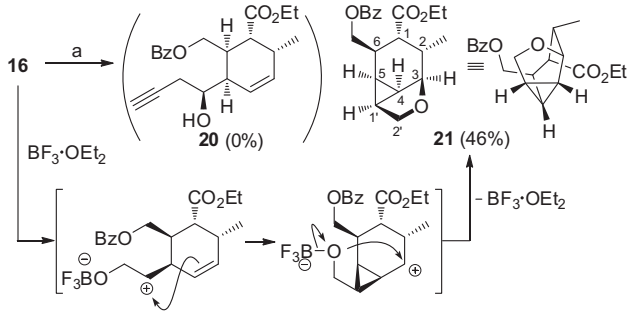


Figure 3. ORTEP drawing of compound **19** showing the right stereochemistry of epoxides.



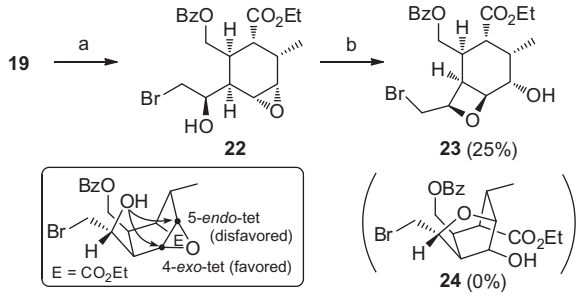
Scheme 6. Rearrangement of the epoxide **16** under Lewis acidic conditions. Reagents and conditions: (a) TMSC≡CLi, $BF_3{\cdot}OEt_2$, THF, −78 °C.

of the α-face compared to the β-face. The α-epoxide **19** gave fortunately diffractable crystals suitable for X-ray crystallography, thus confirming the stereochemistry (Fig. 3).[15,16] With these epoxides in hand, we were ready for cyclization attempts toward the oxygenated bridges of harringtonolide (**1**).

Preliminary trials for opening of the primary epoxide moiety were undertaken. When performed on epoxide **16** in the presence of various nucleophiles, especially alkylating reagents to build the skeleton of **1**, degradation was observed in most cases, except when the reaction was carried out in the presence of lithium trimethylsilylacetylide and $BF_3{\cdot}OEt_2$ in THF. In this case, we were surprised to isolate compound **21** in 46% yields, instead of the expected product **20** (Scheme 6). 2D NMR experiments revealed a highly strained tricyclic cage structure and the absence of acetylide incorporation.[17] A possible mechanism for the formation of **21** is shown in Scheme 6.

The primary epoxide of compound **19**, a potential precursor of the oxygenated system of **1**, was opened in the presence of aqueous KBr and acetic acid in THF, leading to the epoxy-bromohydrine **22** in 94% yield (Scheme 7). Attempts of cyclization in the presence of anhydrous PTSA gave small amounts of the oxetane derivative **23** (25%),[18] resulting from 4-*exo*-tet cyclization, but no trace of the desired 5-membered isomer **24**, as predicted by the Baldwin rules. In this case, we did not observe ring closure of the lactone ring as for compound **11**. These results give interesting insights into the reactivity of such epoxide systems and suggest that an alternative strategy will have to be used for the synthesis of the oxygenated bridges of harringtonolide (**1**).

In conclusion, we have developed a synthetic route allowing for setting up key-stereogenic centers of the cytotoxic norditerpene harringtonolide (**1**). Ring D was made by an asymmetric IMDA reaction leading to a cyclohexene ring (**4a**) bearing appropriate substituents toward the natural product. Functionalization of **4a** led to highly substituted cyclohexane rings (i.e., **11**, **18** or **19**).



Scheme 7. A cyclization attempt toward the oxygenated bridges of harringtonolide. Reagents and Conditions: (a) sat. aq KBr solution, AcOH, THF (1:2:1), rt (94%); (b) PTSA (0.1 equiv), toluene, 80 °C.

During this work, we obtained intermediates (i.e., **11** and **12**) which may be of particular interest for the asymmetric total synthesis of other natural products such as tetrodecamycin (**14**). The reactivity of the epoxide intermediates **16** and **22** was described. Especially, **22** showed preference for 4-*exo*-tet cyclization, leading to oxetane **23**. Our efforts are continuing in order to build the appropriate oxygenated bridges of **1** and adjacent carbocycles.

Acknowledgments

This work and the PhD grant for H.A. have been funded by the Agence Nationale de la Recherche (grant ANR-09-JCJC-0085-01) which is gratefully acknowledged. The Ministère de la Recherche is acknowledged for providing a PhD grant to L.E.

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11. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (d, J = 2.6 Hz, 6H, Si(CH_3)$_2$), 0.98 (s, 9H, SiC(CH_3)$_3$), 1.06-1.10 (m, 12H, SiC(CH_3)$_3$, 2-CH_3), 1.97 (m, 1H, 6-H), 2.08 (m, 1H, 2-H), 2.50 (d, J = 3.5 Hz, 1H, 5-H), 2.83 (q, J = 6.4 Hz, 1H, 1-H), 3.76 (m, 3H, CH_2OTBS, 2'a-H), 3.95 (m, 2H, 1'-H, 2'b-H), 4.37 (m, 2H, 3-H, 4-H), 7.44 (m, 6H, Ph_2Si), 7.66 ppm (m, 4H, Ph_2Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.5 (Si(CH_3)$_2$), 16.4 (2-CH_3), 18.1 (SiC(CH_3)$_3$), 19.2 (Ph_2SiC(CH_3)$_3$), 25.7 (SiC(CH_3)$_3$), 26.8 (Ph_2SiC(CH_3)$_3$), 30.3 (C-2), 36.7 (C-5), 49.9 (C-6), 48.0 (C-1), 63.0 (CH_2OTBS), 65.9 (CH_2OTBDPS), 67.5 (C-4), 71.6 (C-1'), 83.7 (C-3), 127.9 (Ph_2Si), 130.0 (Ph_2Si), 132.7 (Ph_2Si), 135.5 (Ph_2Si), 178.7 ppm (CO_2); HR-MS (ESI+) m/z: calcd for $C_{33}H_{51}O_6Si_2$ [M+H$^+$]: 599.3224; found: 599.3227; IR (film on NaCl) ν: 3390, 2924, 2854, 1778, 1666, 1462, 1377, 1361, 1327, 1211, 1257, 1195, 1111, 1080, 1037, 1006, 972, 925, 837, 740, 702 cm^{-1}; $[\alpha]_D^{25}$ −4 (c = 0.2, $CHCl_3$).
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14. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (d, J = 7.2 Hz, 3H, 2-CH_3), 1.24 (t, J = 7.1 Hz, 3H, CH_3CH_2), 2.38 (m, 1H, 5-H), 2.53 (dd, J = 2.7, 5.0 Hz, 1H, 2'-H), 2.68 (m, 2H, 2-H, 6-H), 2.73 (dd, J = 4.0, 5.0 Hz, 1H, 2'-H), 2.96 (ddd, J = 2.7, 4.0, 10.0 Hz, 1H, 1'-H), 3.07 (dd, J = 6.0, 10.1 Hz, 1H, 1-H), 4.15 (q, J = 7.1 Hz, 2H, CH_3CH_2), 4.63 (d, J = 5.7 Hz, 2H, 6-CH_2OBz), 5.53 (ddd, J = 1.8, 4.5, 10.1 Hz, 1H, 4-H), 5.80 (ddd, J = 1.8, 4.2, 10.0 Hz, 3-H) 7.44 (m, 2H, Bz-H), 7.56 (m, 1H, Bz-H), 8.04 ppm (m, 2H, Bz-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2 (CH_3CH_2), 16.8 (2-CH_3), 31.0 (C-2), 33.0 (C-6), 39.9 (C-5), 42.8 (C-1), 45.1 (C-2'), 51.4 (C-1'), 60.3 (CH_3CH_2), 64.3 (CH_2OBz), 123.3 (C-4), 128.3 (Ph), 129.5 (Ph), 130.3 (Ph), 132.8 (Ph), 133.9 (C-3), 166.2 ($PhCO_2$), 172.7 ppm (CO_2Et); HR-MS (ESI+) m/z: calcd for $C_{20}H_{25}O_5$ [M+H$^+$]: 345.1702; found: 345.1700; IR (KBr pellet) ν: 3444, 3023, 2963, 2924, 2874, 2852, 1725, 1452, 1387, 1375, 1314, 1277, 1180, 1115, 1071, 1029, 714 cm^{-1}; $[\alpha]_D^{25}$ −277 (c = 0.90, MeOH).
15. Compound **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (d, J = 7.2 Hz, 3H, 2-CH_3), 1.21 (t, J = 7.0 Hz, 3H, CH_3CH_2), 2.38 (m, 1H, 5-H), 2.63 (m, 2H, 6-H and 2-H), 2.81 (t, J = 4.3 Hz, 1H, 2'-H), 2.95 (m, 2H, 1-H and 2'-H), 3.08 (m, 1H, 3-H), 3.22 (m, 2H, 4-H and 1'-H), 4.11 (q, J = 7.0 Hz, 2H, CH_3CH_2), 4.57 (m, 2H, CH_2OBz), 7.46 (m, 2H, Ph), 7.56 (m, 1H, Ph), 8.06 ppm (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2 (CH_3CH_2), 13.2 (2-CH_3), 26.3 (C-2), 30.0 (C-6), 39.9 (C-5), 41.6 (C-1), 45.0 (C-2'), 49.2 (C-1'), 54.0 (C-4), 55.6 (C-3), 60.5 (CH_3CH_2), 64.4 (CH_2OBz), 128.3 (Ph), 129.6 (Ph), 130.3 (Ph), 132.8 (Ph), 166.0 ($PhCO_2$), 172.7 ppm (CO_2Et); HR-MS (ESI+) m/z: calcd for $C_{20}H_{25}O_6$ [M+H$^+$]: 361,1651; found: 361,1651; $[\alpha]_D^{25}$ −77 (c = 0.63, CH_3OH).
16. Single crystal X-ray analysis of compound **19**: Intensity data were collected on an Bruker APEX2 four-circle diffractometer by using a graphite monochromated Mo-Kα radiation. The structure was solved by direct methods with SHELXS-86 (Sheldrick, G. M. (1986). SHELXS86. Program for the solution of crystal structures. Univ. of Gottingen, Federal Republic of Germany) refined by full least-squares on F^2 and completed with CRYSTALS (Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. (2001) CRYSTALS Issue 11. Chemical Crystallography Laboratory, Oxford, UK). All non-H atoms were refined with anisotropic displacement parameters and H atoms were simply introduced at calculated positions (riding model with an overall isotropic temperature factor of 0.048). Crystallographic data of compound: $C_{20}H_{24}O_6$, M = 360.41, monoclinic, space group P 2_1 a = 9.6487(10), b = 7.9205(8), c = 12.4344(14) Å, V = 927.32(17) Å^3, Z = 2, D_{calcd} = 1.29 g cm^{-3}, = 0.71073 Å, T = 200(2) K, crystal size = 0.09 · 0.15 · 0.17 mm^3, 9009 reflections measured, 2580 unique (R_{int} = 0.018). The final reliability factors are $R[I>2\sigma(I)]$ = 0.034 and WR_2(all) = 0.093. Crystallographic data (excluding structure factors) for the structure of **19** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 814810. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK fax: + 44 (0) 1233 336033 or e-mail: deposit@ccdc.cam.ac.uk 22. H.D. Flack. Acta Cryst (1983). A39, 876–881.
17. Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (d, J = 7.2 Hz, 3H, CH_3), 1.20 (m, 4H, 5-H, CH_3CH_2), 1.31 (m, 2H, 4-H 1'-H), 1.91 (m, 1H, 2-H), 2.38 (dd, J = 3.0, 10.7 Hz, 1H, 1-H), 2.84 (m, 1H, 6-H), 3.23 (dd, J = 7.4, 11.2 Hz, 1H, 2'-H), 3.63 (dd, J = 5.2, 11.0 Hz, 1H, 2'-H), 4.11 (m, 3H, CH_3CH_2, 3-H), 4.30 (dd, J = 5.1, 10.7 Hz, 1H, BzOCH_2), 4.39 (dd, J = 7.6, 10.7 Hz, 1H, BzOCH_2), 7.45 (t, J = 7.8 Hz, 2H, PhH), 7.57 (m, PhH), 8.05 (m, 2H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.1 (CH_3), 14.2 (CH_3CH_2), 18.3 (C-4), 19.3 (C-5), 21.1 (C-1'), 29.3 (C-6), 36.6 (C-2), 39.7 (C-1), 60.5 (CH_3CH_2), 66.4 (C-2'), 67.6 (BzOCH_2), 67.7 (C-3), 128.4 (Ph), 129.6 (Ph), 130.1 (ipso Ph), 133.0 (Ph), 166.6 (PhCO), 174.1 (CO_2Et); HR-MS (ESI+) m/z: calcd for $C_{20}H_{25}O_5$ [M+H$^+$]: 345.1702; found: 345.1695; IR (film on NaCl) ν: 2963, 2926, 2874, 1734, 1629, 1458, 1288, 1179, 1086, 1030 cm^{-1}; $[\alpha]_D^{25}$ −16 (c = 0.6, MeOH).
18. Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (m, 6H, 2-CH_3, CH_3CH_2), 2.18 (m, 1H, 2-H), 2.50 (ddd, 1H, J = 4.9, 9.6, 11.9 Hz, 1H, 5-H), 2.79 (m, 1H, 6-H), 2.97 (dd, J = 1.1, 5.1 Hz, 1H, 1-H), 3.73 (dd, J = 6.2, 9.2 Hz, 1H, BrCH_2), 3.81 (dd, J = 10.0, 12.0 Hz, 1H, 4-H), 4.18 (m, 3H, BrCH_2, CH_3CH_2), 4.39 (dd, J = 7.7, 11.5 Hz, 1H, BzOCH_2), 4.49 (dd, J = 10.0, 11.0 Hz, 1H, 3-H), 4.56 (dd, J = 5.4, 11.5 Hz, 1H, BzOCH_2), 4.62 (ddd, J = 6.2, 7.6, 9.6 Hz, 1H, 1'-H), 7.49 (m, 2H, PhH), 7.62 (m, 1H, PhH), 8.04 (m, 2H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2 (CH_3CH_2), 17.2 (CH_3), 35.6 (C-6), 37.0 (C-2), 49.7 (C-1), 50.1 (C-5), 57.8 (C-3), 60.9 (CH_3CH_2), 63.0 (BzOCH_2), 71.6 (C-1'), 73.6 (C-2'), 81.5 (C-4), 128.6 (Ph), 129.6 (Ph), 130.7 (ipso Ph), 133.5 (Ph), 166.4 (PhCO), 173.6 (CO_2Et); HR-MS (ESI+) m/z: calcd for $C_{20}H_{26}BrO_6$ [M+H$^+$]: 441.0907; found: 441.1086; IR (film on NaCl) ν: 3425, 2924, 2852, 1724, 1630, 1452, 1273, 1176, 1113, 1026, 713 cm^{-1}.