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An enantiodivergent formal synthesis of paecilomycine A

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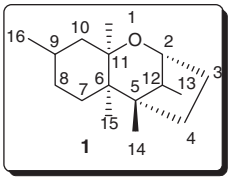
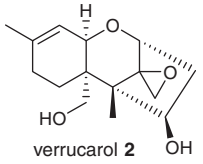
ABSTRACT

A concise, enantiodivergent formal synthesis of (+)-paecilomycine A and its antipode, involving a 1,4-chirality transfer protocol and an intramolecular Pauson–Khand reaction as the key steps is outlined.

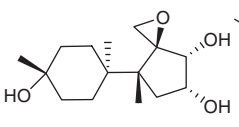
Trichothecenes, based on a tetracyclic sesquiterpenoid framework **1**, are a large and diverse family of mycotoxins produced by various fungal species and are considered important from human health consideration as they are produced on many edible grains like wheat, oats, and maize.[1] Many functional variations on the framework **1** are known and verrucarol **2** is a prototype of this family.[2] Over the years, several biosynthetically mediated structural siblings of trichothecenes like trichotriol **3**,[3] sambucoin **4**,[4] and spirotenuipesine A **5**[5] bearing novel skeletons and diverse bioactivities have been reported. In 2004, a research group led by Ohima isolated[6] a rare class of rearranged tricothecane sesquiterpenoids paecilomycine A–C **6–8** from *Paecilomyces tenuipes* (*Isaria japonica*), a common entomopathogenic fungus described in folk medicine and forming part of health foods in East Asia. The structures of paecilomycine A–C (**6–8**) were elucidated on the basis of extensive 2D NMR analyses and their absolute configuration was determined by MPA ester protocol.[6] Like some of the trichothecenes, paecilomycines **6–8** are also bioactive and (**+**)-paecilomycine A **6** in particular has been shown to exhibit a novel bioactivity profile by promoting neurite outgrowth in rat pheochromocytoma (PC-12) cells at 10 nm concentration.[6] Indeed, it has been shown that (**+**)-**6** biosynthesized and released neurotrophic factors that promoted neuronal differentiation of PC-12 cells and its potency was estimated to be 1000 times higher than that of another promising natural product scabronine G,[7] thereby marking paecilomycine A **6** as a promising lead toward developing drugs against neurodegenerative disorders.



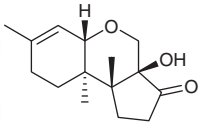
1



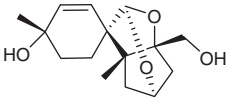
verrucarol **2**



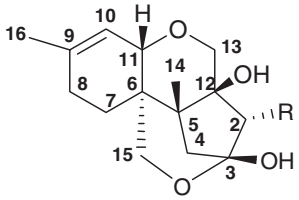
trichotriol **3**



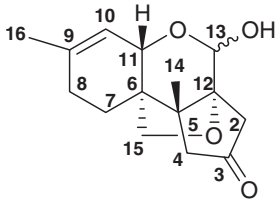
sambucoin **4**



spirotenuipesine A **5**



paecilomycine A **6** : R = H
paecilomycine B **7** : R = OH



paecilomycine C **8**

The interesting structural attributes of **6–8** and the exceptional bioactivity of paecilomycine A **6** mark them as attractive targets for total synthesis and diversity creation. The first total synthesis of racemic paecilomycine A **6** was accomplished in 2007 by

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Danishefsky et al.[8] As a part of our group's[9] continuing interest and engagement with the synthesis of neurotrophically active natural products, we were drawn to paecilomycine natural products and in a recent Letter[10] delineated a concise approach to assemble their tricyclic framework, albeit in racemic form, employing an intramolecular Pauson–Khand reaction[11] as the pivotal step. These studies impelled us to develop an enantioselective approach to the paecilomycine framework and these endeavors have initially led to a formal enantiodivergent synthesis of paecilomycine A **6** which can in principle provide an access to the natural enantiomer as well as its antipode. These efforts are outlined in this Letter.

Our enantioselective approach to paecilomycine natural products emanated from the commercially available (***R***)-3-methylcyclohexanone (99% ee, Aldrich) **9**.[12] A sequential one pot α-carbomethoxylation with ethyl cyanoformate and hydroxymethylation at ambient temperature with aqueous formaldehyde on chiron **9** was followed by the TBS protection of the resultant hydroxyl group to furnish a readily separable diastereomeric mixture of **10a** and **10b** in 7:3 ratio, Scheme 1.[13] The stereochemical outcome of the hydroxymethylation could be substantially modulated in favor of the desired isomer **10a** (9:1) when the formaldehyde quench was carried out at lower temperature (−78 °C). While the temperature mediated diastereoselection leading to **10a** was a welcome outcome in the context of achieving enantioselective access to the natural paecilomycine A series, we persisted in the present study with the conditions that delivered the 7:3 ratio as the intent was to focus on enantiodivergent access to the paecilomycine framework. Gratifyingly, the formation of **10a** and **10b** was regioselective with moderate stereoselectivity attributable to 1,4-stereo-induction by the remote secondary methyl group. Relative stereochemistry at the newly established quaternary carbon center in **10a** and **10b**, though predictable on steric considerations, was secured through stereoselective carbonyl reduction in **10a** under Luche conditions,[14] engendered by the 1,3-stereoinduction by the methyl group, to furnish the diol **11** through concomitant TBS deprotection. Derivatization of **11** to a crystalline bis-3,5-dibromobenzoate **12** and single crystal X-ray structure determination[15] fully secured its formulation (Fig., Scheme 1). Having established a new chiral quaternary center in **10a** and **10b** through chiral induction by the distal methyl group of chiron (***R***)-**9**, we proceeded to erase its original foot print enroute our objective. Toward this end, both the cyclohexanone diastereomers **10a** and **10b** were now individually converted to the corresponding α,β-unsaturated cyclohexenones following the Saegusa protocol[16] involving silylenol ether formation and Pd-mediated dehydrosilylation to furnish enantiomeric enones (**+**)-**13**[13] and (−)-**13**, respectively, Scheme 2. Enones (**+**)-**13** and (−)-**13** were found to be enantiomerically pure (>99% ee) by chiral HPLC,[17] (Scheme 2). Among the enantiomers (**+**)-**13** and (−)-**13**, the former had the absolute configuration (at C6) corresponding to the natural paecilomycines.[6]

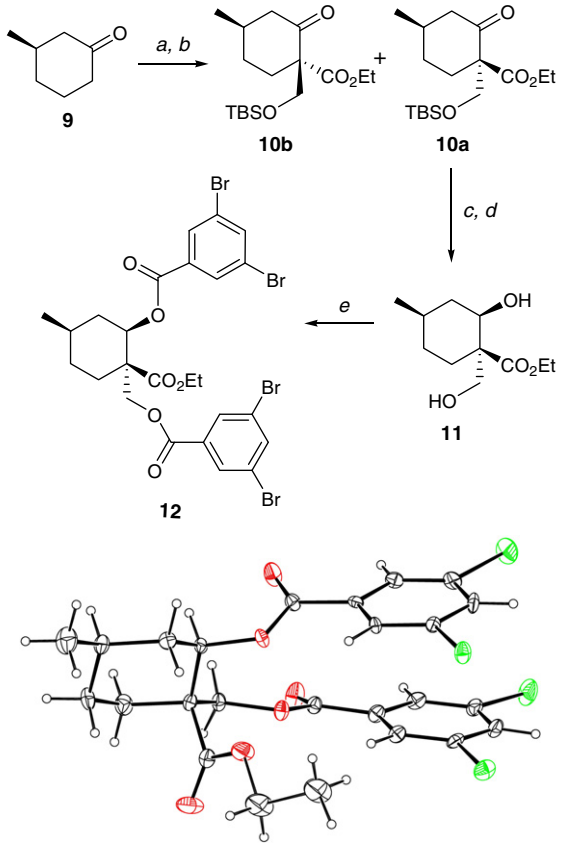
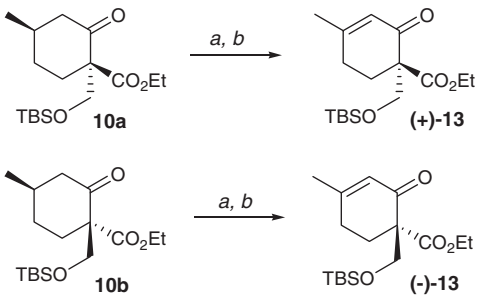


Fig: ORTEP of **12** with 30% probability

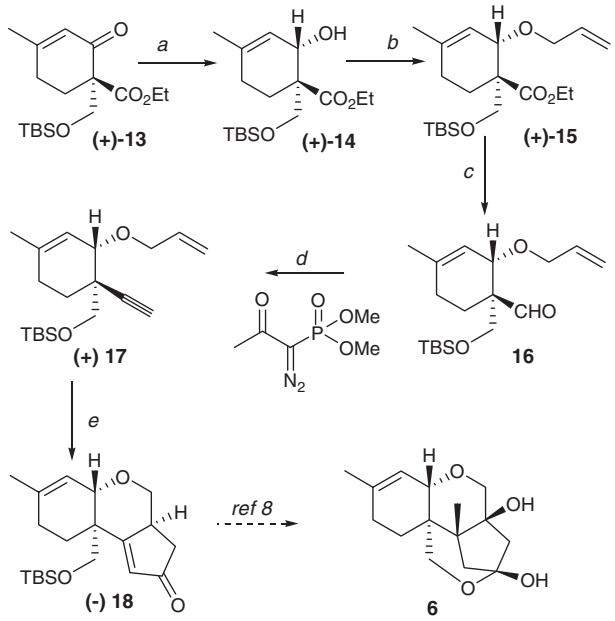
Scheme 1. Reagents and conditions: (a) $CNCO_2Et$, LiHMDS, THF, −78 °C to rt, 2 h, followed by aq HCHO (37–41% w/v), $KHCO_3$, 2 h, 78%; (b) TBSCl, imidazole, CH_2Cl_2, 3 h, 92%; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 15 min, 87%; (d) TBAF, THF, 1 h, 92%; (e) 3,5-dibromobenzoic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 8 h, 85%.

Enone (**+**)-**13** was stereoselectively reduced under Luche conditions[14] to furnish allylic alcohol (**+**)-**14**[13] with the bulky –OTBS protecting group directing the hydride from the opposite β-face. The resulting allylic hydroxyl group in (**+**)-**14** was protected as an allyl ether (**+**)-**15** using allylbromide under carefully calibrated conditions to minimize the formation of a frequently encountered byproduct (<20%) in which TBS and allyl groups have swapped positions.[8,10] The ester moiety in (**+**)-**15** was reduced with DIBAL and the resulting primary alcohol was oxidized with IBX to furnish aldehyde **16**. Aldehyde **16** was smoothly elaborated to enyne (**+**)-**17** using Ohira–Bestmann reagent **18**.[18] The stage was now set for the key intramolecular Pauson–Khand reaction and exposure of (**+**)-**17** to $Co_2(CO)_8$ furnished the tricyclic enone (−)-**18** as a single diastereomer in moderate yield, Scheme 3. Chiral (−)-**18**, so obtained, was found to be spectroscopically identical[13] with the racemic **18** reported by Danishefsky et al.[8] Since, racemic **18** has been converted to paecilomycine A **6** during its first synthesis,[8] our preparation of chiral (−)-**18** constitutes a formal enantioselective synthesis of the natural product.

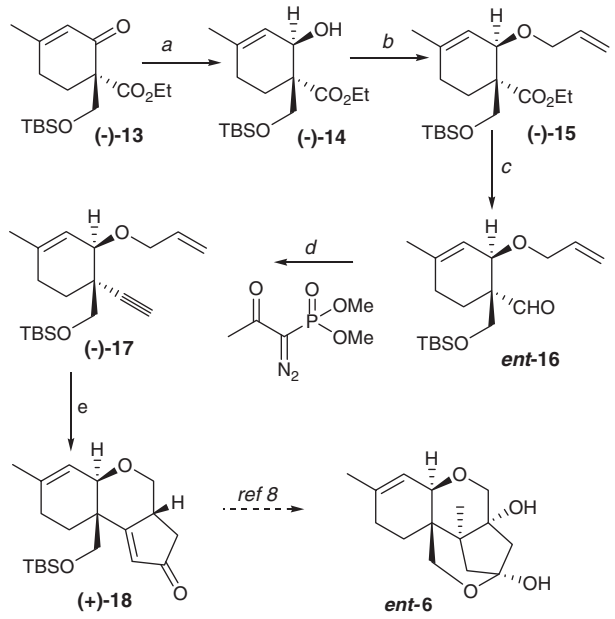
Having accessed the advanced precursor (−)-**18** of (**+**)-paecilomycine A in the natural series, it was of interest to pursue the same objective in the antipodal series. Availability (Scheme 1) of enantiomerically pure (−)-**13** paved the way toward such an enterprise. Thus, stereoselective reduction of (−)-**13** to the allylic alcohol (−)-**14**, protection as the *O*-allylether (−)-**15**, and elaboration of the ester moiety to aldehyde *ent*-**16** were accomplished routinely, Scheme 4. Execution of the Ohira–Bestmann reaction[18] led to the enyne (−)-**17**, the key precursor for the intramolecular Pauson–Khand reaction. Exposure of (−)-**17** to $Co_2(CO)_8$ led to the



Scheme 2. Reagents and conditions: (a) TMSCl, LiHMDS, THF, −78 °C to rt, 1 h; (b) $Pd(OAc)_2$, O_2, DMSO, 55 °C, 72 h, 87% (br sm).



Scheme 3. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 15 min, 86%; (b) allylbromide, NaH, HMPA, TBAI, −15 °C, 3 h, 89%; (c) (i) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, quant; (ii) IBX, THF/DMSO (5:1), 87% (crude); (d) K_2CO_3, MeOH, 6 h, 81%; (e) $Co_2(CO)_8$, 4 Å ms, toluene, reflux, 24 h, 34%.



Scheme 4. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 15 min, 82%; (b) allylbromide, NaH, HMPA, TBAI, −15 °C, 3 h, 85%; (c) (i) DIBAL-H, CH_2Cl_2, 0 °C, 1 h, quant; (ii) IBX, THF/DMSO (5:1), 84% (crude); (d) K_2CO_3, MeOH, 6 h, 79%; (e) $Co_2(CO)_8$, 4 Å ms, toluene, reflux, 24 h, 32%.

tricyclic (**+**)**-18**, spectroscopically identical with the enantiomer (−)**-18** described above and the racemic **18** reported by Danishefsky.[8] Thus, arrival at (**+**)**-18** can be construed as a formal synthesis of *ent*-paecilomycine A **6**.

In conclusion, we have outlined a concise, enantiodivergent strategy that leads to the formal synthesis of (+)-paecilomycine A and its antipode from a single, commercial chiral pool precursor. Considering the important connect between chirality and bioactivity profile, access to both the enantiomeric series related to paecilomycine framework augurs well for exploring the therapeutic potential of their novel scaffold.

Acknowledgments

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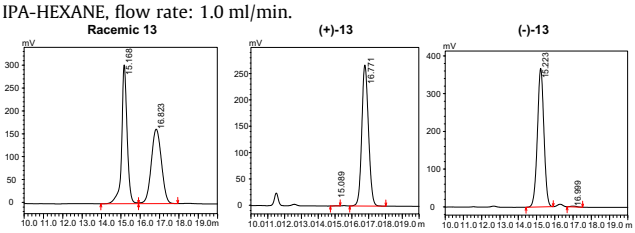
12. Preparation of (**9**): (a) Adams, R.; Smith, C. M.; Loewe, S. *J. Am. Chem. Soc.* **1942**, 2087–2089; (b) Djerassi, C.; Krakower, G. W. *J. Am. Chem. Soc.* **1958**, 237–242.
13. All new compounds were characterized on the basis of their spectroscopic data (IR, ^1H, ^{13}C, mass, HRMS). Spectral data for some of the key compounds are as follows: **10a:** $[\alpha]_D^{20}$ +64.80 (*c* 1.65, $CHCl_3$); IR (neat): 2953, 2861, 1714, 1648, 1519, 1461, 1252, 1098, 839, 778. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.13 (q, *J* = 7.0 Hz, 2H), 4.02 (d, *J* = 10.0 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 2.59–2.57 (m, 1H), 2.31 (d, *J* = 13.0 Hz, 1H), 2.03 (t, *J* = 13.0 Hz, 1H), 1.80–1.71 (m, 2H), 1.51–1.40 (m, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.80 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.4, 169.8, 66.0, 61.6, 61.1, 49.3, 35.0, 32.5, 30.8, 25.6 (3C), 22.2, 18.0, 14.0, −5.8 (2C). MS (ESI) *m/z* 351 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_4SiNa$ $(M+Na)^+$ = 351.1967, found 351.1954. Compound **10b:** $[\alpha]_D^{20}$ −11.0 (*c* 0.60, $CHCl_3$); IR (neat): 2932, 1712, 1518, 1462, 1249, 1102, 839, 778. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.19–4.13 (m, 2H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.82 (d, *J* = 10.0 Hz, 1H), 2.52 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.39–2.35 (m, 1H), 2.21 (br s, 1H), 2.10 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.98–1.91 (m, 2H), 1.54–1.49 (m, 1H), 1.23 (t, *J* = 8.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.1, 170.5, 65.1, 62.6, 61.1, 47.8, 32.2, 28.7, 28.3, 25.6 (3C), 19.8, 18.1, 14.0, −5.7, −5.8. MS (ESI) *m/z* 351 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_4SiNa$ $(M+Na)^+$ = 351.1967, found 351.1953. Compound (+)-**13**: $[\alpha]_D^{20}$ +27.7 (*c* 1.0, $CHCl_3$); IR (neat): 2950, 2890, 2863, 2361, 1737, 1682, 1519, 1250, 1110, 842. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.83 (s, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.03 (d, *J* = 9.6 Hz, 1H), 3.84 (d, *J* = 9.6 Hz, 1H), 2.62–2.44 (m, 2H), 2.29–2.19 (m, 1H), 2.15–2.04 (m, 1H), 1.94 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 193.6, 169.7, 161.8, 126.1, 65.3, 61.0, 57.9, 28.6, 27.9, 25.9 (3C), 24.3, 18.3, 14.2, −5.5 (2C). MS (ESI) *m/z* 349 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{30}O_4SiNa$ $(M+Na)^+$ = 349.1806, found 349.1813. Compound (−)-**13:** $[\alpha]_D^{20}$ −31.7 (*c* 1.0, $CHCl_3$); (+)-**14:** $[\alpha]_D^{20}$ +51.36 (*c* 0.88, $CHCl_3$); IR (neat): 2930, 2857, 1726, 1516, 1464, 1249, 1096, 840, 777. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.48 (br d, *J* = 2.1 Hz, 1H), 4.48 (br d, *J* = 2.1 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.72 (d, *J* = 10.0 Hz, 1H), 1.92 (t, *J* = 6.0 Hz, 2H), 1.85–1.69 (m, 2H), 1.67 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.8, 137.4, 122.7, 67.0, 65.3, 60.5, 51.2, 27.3, 25.6 (3C),

23.5, 23.1, 18.0, 14.1, −5.7, −5.8. MS (ESI) *m/z* 351 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}O_4SiNa$ $(M+Na)^+$ = 351.1967, found 351.1952. Compound (−)-**14:** $[\alpha]_D^{20}$ −47.63 (*c* 1.0, $CHCl_3$); (+)-**15**: $[\alpha]_D^{20}$ +137.23 (*c* 1.0, $CHCl_3$); IR (neat): 2931, 2858, 2363, 1738, 1516, 1464, 1250, 1172, 1095, 842, 776. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.87 (ddd, *J* = 16.0, 11.0, 6.0 Hz, 1H), 5.63 (br d, *J* = 3.0 Hz, 1H), 5.22 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.14–4.04 (m, 4H), 4.02–3.96 (m, 1H), 3.91 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 9.0 Hz, 1H), 1.96–1.91 (m, 2H), 1.83–1.76 (m, 1H), 1.73–1.69 (m, 1H), 1.67 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.9, 138.1, 135.5, 121.0, 116.3, 71.8, 71.1, 65.9, 60.1, 52.0, 27.7, 25.7 (3C), 23.4, 23.1, 18.0, 14.1, −5.6, −5.8. MS (ESI) *m/z* 391 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{36}O_4SiNa$ $(M+Na)^+$ = 391.2280, found 391.2281. Compound (−)**15**: $[\alpha]_D^{20}$ −140.10 (*c* 1.0, $CHCl_3$); **(+)17:** $[\alpha]_D^{20}$ +132.30 (*c* 0.8, $CHCl_3$); IR (neat): 3308, 2930, 2858, 1741, 1693, 1516, 1464, 1253, 1112, 841, 777, 633. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.92 (ddd, *J* = 16.2, 10.5, 5.7 Hz, 1H), 5.57–5.56 (m, 1H), 5.25 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 4.21–4.10 (m, 2H), 3.85 (d, *J* = 4.8 Hz, 1H), 3.80 (d, *J* = 9.6 Hz, 1H), 3.54 (d, *J* = 9.0 Hz, 1H), 2.28–2.17 (m, 1H), 1.99 (s, 1H), 1.92 (br s, 1H), 1.77–1.68 (m, 1H), 1.72 (s, 3H), 1.48 (m, 1H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 135.6, 120.1, 116.4, 87.4, 74.6, 71.4, 69.2, 66.6, 41.4, 27.7, 25.9 (3C), 25.1, 23.5, 18.4, −5.3 (2C). MS (ESI) *m/z* 343 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_2SiNa$ $(M+Na)^+$ = 343.2069, found 343.2076. Compound (−)-**17:** $[\alpha]_D^{20}$ −134.14 (*c* 1.0, $CHCl_3$); (−)-**18:** $[\alpha]_D^{20}$ −73.61 (*c* 0.16, $CHCl_3$); IR (neat): 2927, 2856, 2364, 1741, 1707, 1647, 1516, 1463, 1094, 841. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.83 (br s, 1H), 5.28 (br s, 1H), 4.35 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.96 (d, *J* = 10.5 Hz, 1H), 3.76 (d, *J* = 10.5 Hz, 1H), 3.71 (br s, 1H), 3.31–3.26 (m, 1H), 3.18 (dd, *J* = 21, 10.8 Hz, 1H, 2.45 (dd, *J* = 18.6, 6.6 Hz, 1H), 2.27 (dd, *J* = 12.6, 5.7 Hz, 1H), 2.16–2.00 (m, 2H), 1.88 (dd, *J* = 18.3, 1.8 Hz, 1H), 1.70 (s, 3H), 1.66–1.51 (m, 1H), 0.82 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.7, 186.0, 136.3, 126.5, 121.1, 81.4, 75.1, 60.6, 46.4, 38.6, 37.7, 27.6, 25.9 (3C), 24.5, 22.9, 18.3, −5.4 (2C). MS (ESI) *m/z* 371 $(M+Na)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{32}O_3SiNa$ $(M+Na)^+$ = 371.2018, found 371.2028. Compound **(+)-18:** $[\alpha]_D^{20}$ +75.32 (*c* 0.16, $CHCl_3$).

14. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
15. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 294 K using graphite monochromated Mo Kα radiation (λ = 0.7107Å). The data were reduced by *SAINTPLUS*; the crystal structures were solved by direct methods using *SHELXS97* and refined by full-matrix least-squares method using *SHELXL97*. Crystal data for 3,5-dibromobenzoate **12**: $C_{25}H_{24}Br_4O_6$, *M* = 740.08, orthorhombic, $P2_12_12_1$, *a* = 9.3505(15), *b* = 14.166(2), *c* = 20.060(3) Å, *V* = 2657.2(7) $Å^3$, *Z* = 4, ρ_{calcd} = 1.850 mg m^{-3}, 23,303 reflections measured, 4669 unique, 3471 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final *R* = 0.0519 and *wR* = 0.0997 and GOF = 0.971. CCDC 844353.
16. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
17. Chiral HPLC: Column: chiral pak IC 250X4.6 mm, 5microns, mobile phase: 3% IPA-HEXANE, flow rate: 1.0 ml/min.



18. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564; (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–552; (c) Seyferth, D.; Marmor, R. S.; Hibert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386; (d) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997–4998.