A Practical Synthesis of [(1*S*,3*S*)-3-Aminocyclohexyl]methanol and 2-[(1*S*,3*S*)-3-Aminocyclohexyl]propan-2-ol, Useful Intermediates for the Preparation of Novel *m*PGES-1 Inhibitors

Daniel P. Walker,*[a] Steven E. Heasley,[a] Allison MacInnes,[a] Tizah Anjeh,[b] Hwang-Fun Lu,[a] Yvette M. Fobian,[a] Joe T. Collins,[a] Michael L. Vazquez,[a] Michael K. Mao[b]

[a] Pfizer Worldwide Medicinal Chemistry, Pfizer, Inc., 700 Chesterfield Parkway West, Chesterfield, MO 63017, USA
Fax +1(860)6860013; E-mail: daniel.p.walker.pfizer@gmail.com

[b] Pfizer Worldwide Pharmaceutical Sciences, Pfizer, Inc., 700 Chesterfield Parkway West, Chesterfield, MO 63017, USA

Received 20 July 2011

Abstract: Microsomal prostaglandin E2 synthase-1 (*m*PGES-1) is a novel therapeutic target for the treatment of inflammation and pain. During the course of studies aimed at the identification of a suitable *m*PGES-1 inhibitor for clinical development, a need arose for preparing enantiomerically enriched amino alcohols (*S*,*S*)-**2** and (*S*,*S*)-**3**. Described herein, a concise synthesis of (*S*,*S*)-**2** and (*S*,*S*)-**3** has been developed wherein both amino alcohols are derived from a commercially available, low-cost starting material.

Key words: carbocycles, heterocycles, anti-inflammatory agents, chiral resolution, rearrangement

Inducible microsomal prostaglandin E_2 synthase-1 (*m*PGES-1), the predominate synthase involved in cyclooxygenase-2 (COX-2) mediated PGE_2 production, is a novel therapeutic target of considerable interest in the treatment of inflammation and pain.[1] We have been interested in preparing substituted benzoxazoles of type **1** as *m*PGES-1 inhibitors (Figure 1).[2] During the course of studies aimed at the identification of a suitable inhibitor for clinical development, a need arose for obtaining hundreds of grams of enantiomerically enriched amino alcohols (*S*,*S*)-**2** and (*S*,*S*)-**3**. Due to the *trans*-1,3-relationship between the substituents on (*S*,*S*)-**2** and (*S*,*S*)-**3**, one of the substituents on the cyclohexyl ring occupies a presumably thermodynamically unfavorable axial orientation, which could make the synthesis more challenging.

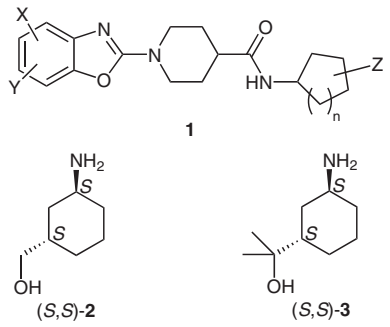
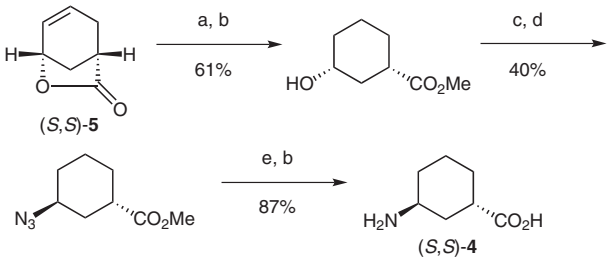


Figure 1 General structure of novel *m*PGES-1 inhibitors (**1**) and new synthetic targets (*S*,*S*)-**2** and (*S*,*S*)-**3**

While no prior studies on the synthesis of either (*S*,*S*)-**2** or (*S*,*S*)-**3** have appeared in the literature, Zhu et al. prepared the related carboxylic acid (*S*,*S*)-**4** in six steps from enantiomerically enriched (97% ee) lactone (*S*,*S*)-**5** (Scheme 1);[3] the latter compound being prepared in four steps from commercially available material.[4] While (*S*,*S*)-**4** presumably could be converted into desired (*S*,*S*)-**2**, the existing synthesis of (*S*,*S*)-**4** is lengthy, and the starting dienophile is expensive. Based on prior work by Murahashi,[5] Zhu et al. attempted to shorten their route via a direct S_N2 opening of lactone (*S*,*S*)-**5** with sodium azide. Unfortunately, partial racemization occurred during the reaction, presumably due to ring opening via a competing S_N2' pathway.[3] We detail below a concise synthesis of (*S*,*S*)-**2** and (*S*,*S*)-**3**, of which both compounds are derived from a low cost starting material.



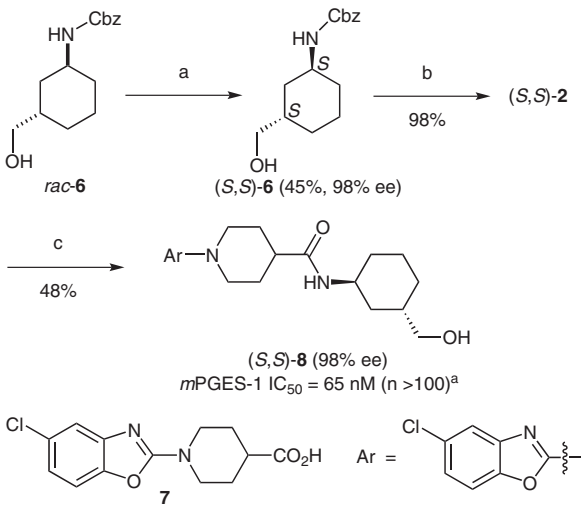
Scheme 1 Zhu's synthesis of (*S*,*S*)-**4** based on Trost's enantiomerically enriched lactone (*S*,*S*)-**5**. *Reagents and conditions*: (a) Na_2CO_3, MeOH, r.t.; (b) H_2, Pd/C, MeOH; (c) TsCl, py, CH_2Cl_2; (d) NaN_3, DMF, 80 °C; (e) LiOH, THF–MeOH–H_2O, 40 °C; acidic workup.

Our initial API requirements for (*S*,*S*)-**2** were met via the synthetic sequence outlined in Scheme 2. Thus, resolution of Cbz-protected amino alcohol *rac*-**6**, which was purchased from a vendor,[6] using chiral super critical fluid chromatography (SFC)[7] afforded enantiomerically enriched carbamate (*S*,*S*)-**6**[8] (98% ee). Hydrogenolysis of the Cbz-group in (*S*,*S*)-**6** gave rise (98%) to the desired amine (*S*,*S*)-**2**.[9,10] HATU-mediated coupling of amine (*S*,*S*)-**2** with carboxylic acid **7**[2] afforded amide (*S*,*S*)-**8**.[11] Compound (*S*,*S*)-**8** was shown to be a potent inhibitor in our *m*PGES-1 enzyme assay (Scheme 2). Conversely, enantiomer (*R*,*R*)-**8**[12] was 75-fold less active, displaying only weak activity. The absolute configuration at C(1) and C(3) on the cyclohexyl ring in (*S*,*S*)-**8** was unambiguously

SYNLETT 2011, No. 20, pp 2959–2962
Advanced online publication: 11.11.2011
DOI: 10.1055/s-0031-1289884; Art ID: S06711ST

established as (1*S*,3*S*) via X-ray crystallography (Figure 2).[13]

The option of purchasing carbamate *rac*-**6** was convenient as it provided access to gram quantities of enantiomerically pure amino alcohol (*S*,*S*)-**2**; however, this tactic did not represent a long-term solution for meeting our API needs. The high cost of *rac*-**6**, coupled with long lead times, meant sourcing this material was no longer practical; hence, we sought to develop a practical synthesis of *rac*-**6**, capable of delivering hundreds of grams of API.



Scheme 2 *Reagents and conditions*: (a) resolution, SFC, Chiral Pak AD-H 250 column (EtOH–CO_2, 1:3, 40 °C); (b) H_2, 10% Pd/C (cat.), MeOH, 50 psi, 16 h; (c) carboxylic acid **7** (1.0 equiv), amine **2** (1.2 equiv), HATU (1.2 equiv), *i*-Pr_2NEt (5.0 equiv), DMF, r.t., 16 h. [a] *m*PGES-1 enzyme inhibition assay. Numbers indicate IC_{50} values generated from 10-point concentration response relationships in duplicate, *n* values in parentheses denotes number of iterations. For enzyme assay conditions, see ref. 14.

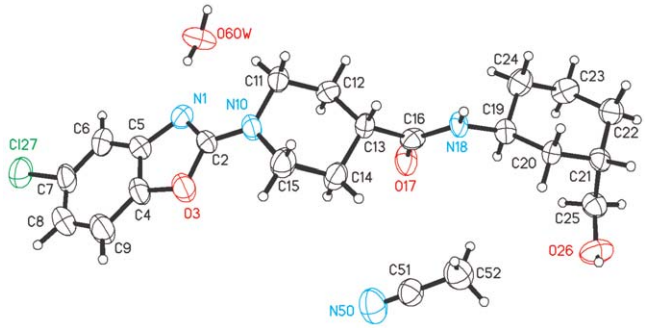
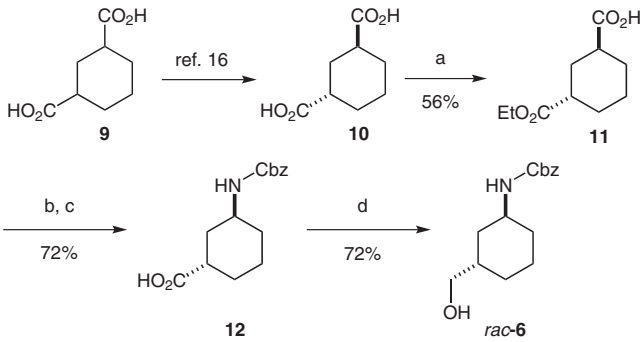


Figure 2 ORTEP diagram of compound (*S*,*S*)-**8**



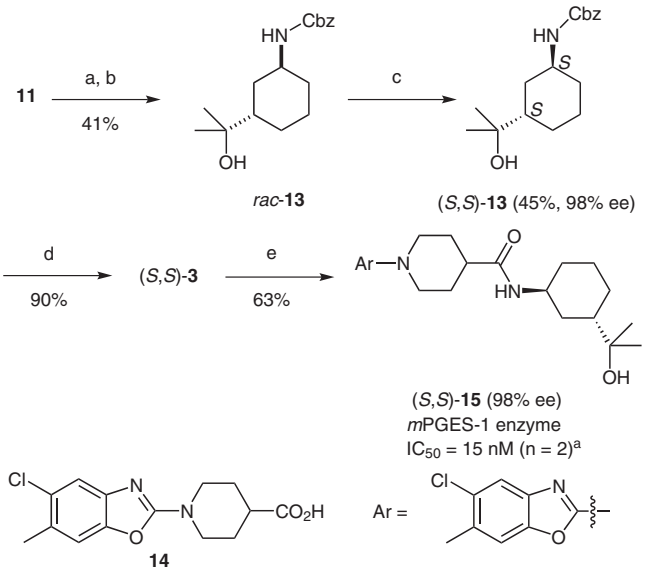
Scheme 3 *Reagents and conditions*: (a) EtOH (1.0 equiv), concd HCl (cat.), 80 °C, 4 h; (b) DPPA (1.0 equiv), Et_3N (1.1 equiv), toluene, 70 °C, 1 h; BnOH (1.05 equiv), Et_3N (1.1 equiv), 80 °C, 5 h; (c) LiOH·H_2O (5.0 equiv), THF–MeOH–H_2O (6:3:1), r.t., 5 h; (d) BH_3·THF (2.2 equiv), THF, –5 °C, 4 h.

Our synthesis of *rac*-**6** commenced from dicarboxylic acid **9**, a low cost, commercially available mixture of *cis*- and *trans*-isomers (Scheme 3).[15] The *trans*-isomer can be efficiently isolated in high purity using the procedure of Skita and Rossler.[16] Monoesterification of *trans*-isomer **10** afforded ester **11**.[17] Under these conditions, no epimerization to the corresponding *cis*-isomer was seen. Curtius rearrangement of carboxylic acid **11** and trapping of the intermediate isocyanate with benzyl alcohol led to the corresponding carbamate. Subsequent saponification of the ester with lithium hydroxide gave rise (72%) to carboxylic acid **12**. Again, under these conditions, no epimerization to the *cis*-isomer occurred. It should be mentioned that in a prior study Hewgill and Jefferies utilized a Schmidt reaction to convert dicarboxylic acid **10** into the related amino acid *rac*-**4**.[18] Unfortunately, this procedure utilizes the highly toxic and potentially explosive hydrazoic acid, which was seen as a significant drawback to our API needs.

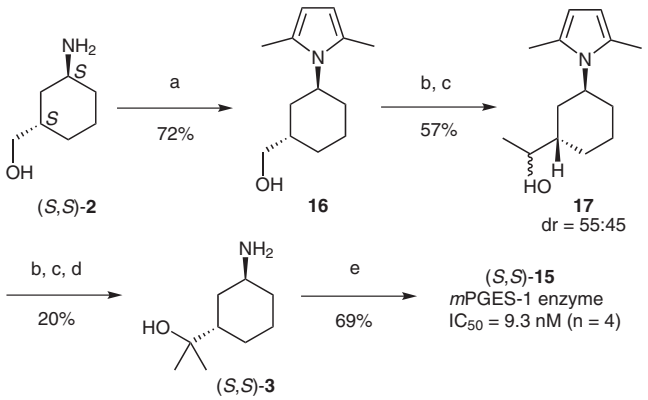
Desired alcohol *rac*-**6** was realized in 72% yield via borane reduction of carboxylic acid **12** (Scheme 3). The spectral properties of *rac*-**6**, prepared according to Scheme 3, were identical to an authentic sample of *rac*-**6**. Over 100 grams of *rac*-**6** was prepared according to Scheme 3.

Enantiomerically enriched amino alcohol (*S*,*S*)-**3** was also prepared from commercial dicarboxylic acid **9** (Scheme 4). Toward this end, treatment of monoester **11** with methyl magnesium bromide, followed by subsequent Curtius rearrangement of the carboxylic acid led to tertiary alcohol *rac*-**13**. Resolution of *rac*-**13** using SFC afforded enantiomerically enriched alcohol (*S*,*S*)-**13**.[19] Hydrogenolysis of the benzyloxycarbonyl group in (*S*,*S*)-**13** gave rise (90%) to the desired amino alcohol [(*S*,*S*)-**3**].[9,20] Over 100 grams of *rac*-**13** was prepared via this synthetic route. HBTU-Mediated coupling of amine (*S*,*S*)-**3** with carboxylic acid **14**[2] gave rise to amide (*S*,*S*)-**15**.[21] Compound (*S*,*S*)-**15** was a potent inhibitor of *m*PGES-1 in the enzyme assay (Scheme 3); the corresponding enantiomer [(*R*,*R*)-**15**] was ca. 50-fold less potent.[22]

The absolute configuration of (*S*,*S*)-**3** was established based on the synthesis shown in Scheme 5. Thus, condensation of enantiomerically enriched amine (*S*,*S*)-**2** with acetyl acetone afforded dimethylpyrrole **16**. Oxidation (TPAP, NMO) of the alcohol gave the corresponding aldehyde. Treatment of the aldehyde with methyl magnesium bromide led to secondary alcohol **17**. The addition to the aldehyde was essentially nonselective under these conditions (dr = 55:45). Oxidation of the alcohol with TPAP and NMO gave rise (76%) to the corresponding methyl ketone. Subjection of the ketone to methyl Grig-



Scheme 4 *Reagents and conditions*: (a) MeMgBr (3.0 M solution in Et_2O, 3.15 equiv), THF, 0 °C→r.t., 16 h; (b) DPPA (1.0 equiv), Et_3N (1.1 equiv), toluene, 70 °C, 1 h; BnOH (1.05 equiv), Et_3N (1.1 equiv), 80 °C, 5 h; (c) resolution, SFC chromatography, Chiral Pak IA 250 column (EtOH–*i*-PrOH-CO_2, 1:1:6, 40 °C); (d) H_2, 10% Pd/C, MeOH, 50 psi, r.t., 18 h; (e) carboxylic acid **14** (1.0 equiv), amine **3** (1.2 equiv), HBTU (1.2 equiv), Et_3N (1.5 equiv), DMF, r.t., 16 h. [a] *m*PGES-1 enzyme inhibition assay. Numbers indicate IC_{50} values generated from 10-point concentration response relationships in duplicate, *n* values in parentheses denotes number of iterations. For enzyme assay conditions, see ref. 14.



Scheme 5 *Reagents and conditions*: (a) acetyl acetone (1.1 equiv), AcOH (cat.), toluene, reflux, Dean–Stark, 2 h; (b) TPAP (cat.), NMO (1.5 equiv), 4 Å mol. sieves, CH_2Cl_2, 2 h; (c) MeMgBr (3.0 M soln in Et_2O, 1.2 equiv), Et_2O, 0 °C, 30 min; (d) $NH_2OH{\cdot}HCl$ (20 equiv), Et_3N (10 equiv), *i*-PrOH–H_2O (2.5 mL, 4:1), reflux, 6 h; NaOH (4.0 equiv), 0 °C, 16 h; (e) carboxylic acid **14** (1.0 equiv), amine (*S*,*S*)-**3** (1.2 equiv), HBTU (1.2 equiv), Et_3N (1.5 equiv), DMF, r.t., 16 h.

nard afforded the tertiary alcohol in 83% yield. Subsequent hydrolysis of the dimethyl pyrrole gave amine (*S*,*S*)-**3** in low yield. Coupling (*S*,*S*)-**3** with carboxylic acid **14** afforded (*S*,*S*)-**15**. Using chiral SFC conditions similar to above, (*S*,*S*)-**15**, prepared according to Scheme 5, co-eluted with (*S*,*S*)-**15** prepared according to Scheme 4. In addition, the biological activity of (*S*,*S*)-**15**, prepared according to Scheme 5, was identical to the activity of (*S*,*S*)-**15** prepared according to Scheme 4. Based on these data, it is highly likely that the absolute configuration at C(1) and C(3) on the cyclohexyl ring of (*S*,*S*)-**15** is (1*S*,3*S*).

In summary, we have described a concise racemic synthesis of two amino alcohols, which were resolved by chiral chromatography to afford enantiomerically enriched (*S*,*S*)-**2** and (*S*,*S*)-**3**. Those key intermediates were used for the preparation of potent *m*PGES-1 inhibitors. Both amino alcohols were derived from the same low cost starting material. Over 100 grams of (*S*,*S*)-**2** and (*S*,*S*)-**3** were prepared utilizing the described chemistry.

Acknowledgment

We thank Jon Bordner and Ivan Samardjiev of Pfizer for generating x-ray crystallographic data on (*S*,*S*)-**8**. We thank Gina Jerome of Pfizer for generating *m*PGES-1 enzyme inhibition data.

References and Notes

(1) (a) Koeberle, A.; Werz, O. *Curr. Med. Chem.* **2009**, *16*, 4274. (b) Samuelsson, B.; Morganstern, R.; Jakobsson, P.-J. *Pharmacol. Rev.* **2007**, *59*, 207.
(2) A full account on the design, synthesis, SAR and in vivo activity of type-**1** compounds will be published elsewhere in due course.
(3) Hu, Y.; Yu, S.-L.; Yang, Y.-J.; Zhu, J.; Deng, J.-G. *Chin. J. Chem.* **2006**, 795.
(4) Trost, B. M.; Kondo, Y. *Tetrahedron Lett.* **1991**, 1613.
(5) Murahashi, S.-I.; Tanigushi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.
(6) Our vendor supplied hundreds of grams of *rac*-**4** for ca. $100/gram with a lead time of 5–7 weeks.
(7) Bhatt, H. S.; Patel, G. F.; Vekariya, N. V.; Jadav, S. K. *J. Pharm. Res.* **2009**, *2*, 1606..
(8) Analytical data for (*S*,*S*)-**6**: Peak 2; white solid; mp 69–71 °C; $[\alpha]^{25}_D$ 0.2 (*c* = 1.5, MeOH). ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.26–7.40 (m, 5 H), 5.10 (s, 2 H), 3.77–3.85 (m, 1 H), 3.41 (d, *J* = 6.4 Hz, 2 H), 1.76–1.83 (m, 1 H), 1.64–1.75 (m, 2 H), 1.53–1.64 (m, 4 H), 1.38–1.45 (m, 1 H), 1.14–1.23 (m, 1 H). ^{13}C NMR (125 MHz, MeOH-d_4): δ = 158.3, 138.6, 129.6, 129.1, 129.0, 67.37, 67.34, 47.67, 36.37, 34.74, 32.37, 29.34, 21.42. LRMS (ESI): *m/z* = 264 $[M + H]^+$.
(9) Amines **2** and **3** were found to absorb carbon dioxide and darken with age. We found it more convenient to store these amines as the corresponding carbamates, **6** and **13**, which were shelf stable for more than a year, and convert them into **2** and **3** on an add-need basis.
(10) Analytical data for (*S*,*S*)-**2**: ^{1}H NMR (400 MHz, MeOH-d_4): δ = 3.43 (d, *J* = 6.7 Hz, 2 H), 3.02–3.09 (m, 1 H), 1.79–1.90 (m, 1 H), 1.49–1.70 (m, 7 H), 1.19–1.30 (m, 1 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 66.54, 47.42, 35.99, 35.42, 33.33, 28.87, 20.83. LRMS (ESI): *m/z* = 130.1 $[M + H]^+$.
(11) Analytical data for (*S*,*S*)-**8**: 98% ee (analytical chiral HPLC); $[\alpha]^{25}_D$ –6.4 (*c* = 1.8, MeOH). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.78 (br d, *J* = 7.4 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 7.23 (d, *J* = 1.96 Hz, 1 H), 7.02 (dd, *J* = 8.2, 1.95 Hz, 1 H), 4.26–4.32 (m, 2 H), 3.96–4.03 (m, 1 H), 3.43 (d, *J* = 6.6 Hz, 2 H), 3.20 (td, *J* = 13.3, 3.1 Hz, 2 H), 2.57 (tt, *J* = 11.3, 3.9 Hz, 1 H), 1.72–1.91 (m, 5 H), 1.63–1.72 (m, 2 H), 1.53–1.62 (m, 4 H), 1.37–1.46 (m, 1 H), 1.17–1.26 (m, 1 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 175.3, 163.2, 147.4, 144.2, 129.4, 120.5, 115.3, 109.5, 65.81, 45.16, 44.80, 44.70, 42.11, 42.06, 35.24, 33.03, 30.79, 28.04, 27.93, 20.17. LRMS (ESI): *m/z* = 392 $[M + H]^+$.

(12) Compound (*R*,*R*)-**8** (98% ee) was prepared using similar conditions to that described for the preparation of (*S*,*S*)-**8** except (*R*,*R*)-**6** (98% ee) was used in place of (*S*,*S*)-**6**.
(13) Data for compound (*S*,*S*)-**8** (crystals from MeCN) were collected on a Bruker APEX diffractometer at Pfizer Groton laboratories, and all crystallographic calculations were facilitated by the SHELXIL system: $C_{20}H_{26}N_3O_3Cl{\cdot}MeCN{\cdot}H_2O$; FW = 450.96; monoclinic; space group P2 (1); unit cell dimensions: a = 5.0339 (3) Å, b = 12.3675 (5) Å, c = 18.4354 (9) Å; volume = 1145.14 (10) Å^3; Z = 2; D_{calcd} = 1.308 Mg/m^3; absorption coefficient = 1.772 mm^{-1}; F(000) = 480; GOF on F2 = 1.029; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0393, wR_2 = 0.1026.
(14) Wang, J.; Limburg, D.; Carter, J.; Mbalaviele, G.; Gierse, J.; Vazquez, M. *Bioorg. Med. Chem. Lett.* **2010**, 1604.
(15) Dicarboxylic acid **7** is sold as a mixture of *cis*- and *trans*-isomers (*cis*/*trans* = ca. 3:1), and is available in bulk quantities from various vendors for $0.60/gram; alternatively, it can be efficiently prepared via catalytic hydrogenation of isophthalic acid, see: Freifelder, M.; Dunnigan, D. A.; Baker, E. J. *J. Org. Chem.* **1966**, *31*, 3438.
(16) Skita, A.; Rossler, R. *Chem. Ber.* **1939**, *72*, 265.
(17) Hart, R. W.; Gibson, R. E. *J. Med. Chem.* **1975**, *18*, 323.
(18) Hewgill, F. R.; Jefferies, P. R. *J. Chem. Soc.* **1955**, 2767.
(19) Analytical data for (*S*,*S*)-**13**: clear oil; Peak 2 (98% ee); $[\alpha]^{25}_D$ –10 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, MeOH-d_4): δ = 7.26–7.38 (m, 5 H), 6.92 (br d, J = 6.59 Hz, 1 H), 5.07 (ABq, J_{AB} = 15.0 Hz, $\Delta\nu_{AB}$ = 12.0 Hz, 2 H), 3.92–3.98 (m, 1 H), 1.91–1.97 (m, 1 H), 1.82 (d, J = 12.7 Hz, 1 H), 1.74 (d, J = 12.9 Hz, 1 H), 1.58–1.64 (m, 1 H), 1.47–1.58 (m, 2 H), 1.43 (tt, J = 13.2, 3.4 Hz, 1 H), 1.27 (td, J = 13.2, 3.5 Hz, 1 H), 1.11 (s, 3 H), 1.10 (s, 3 H), 1.02 (qd, J = 12.3, 3.8 Hz, 1 H). ^{13}C NMR (125 MHz, MeOH-d_4): δ = 158.4, 138.6, 129.6, 129.1, 129.0, 73.24, 67.37, 43.92, 32.65, 31.35, 28.19, 27.03, 26.93, 25.41, 22.09. LRMS (ESI): m/z = 313.9 [M + Na]$^+$.
(20) Analytical data for (*S*,*S*)-**3**: clear oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.80–4.25 (br s, 2 H), 3.24–3.28 (m, 1 H), 1.65–1.76 (m, 2 H), 1.48–1.61 (m, 3 H), 1.40–1.48 (m, 1 H), 1.34 (tt, J = 13.7, 3.9 Hz, 1 H), 1.18 (td, J = 12.9, 3.5 Hz, 1 H), 1.00 (s, 6 H), 0.89 (qd, J = 12.1, 3.5 Hz, 1 H). LRMS (ESI): m/z = 158.1 [M + H]$^+$.
(21) Analytical data for (*S*,*S*)-**15**: white solid; 98% ee (analytical chiral HPLC). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.57 (br d, J = 7.69 Hz, 1 H), 7.39 (s, 1 H), 7.29 (s, 1 H), 4.11–4.15 (m, 2 H), 3.99–4.03 (m, 1 H), 3.92 (s, 1 H), 3.09–3.15 (m, 2 H), 2.53–2.57 (m, 1 H), 2.34 (s, 3 H), 1.71–1.79 (m, 4 H), 1.54–1.64 (m, 3 H), 1.46–1.53 (m, 3 H), 1.26–1.34 (m, 1 H), 1.08–1.15 (m, 1 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.87–0.95 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.1, 162.4, 147.3, 142.5, 128.1, 126.9, 115.4, 110.8, 70.46, 44.97, 44.08, 42.00, 40.69, 30.89, 29.64, 27.86, 27.76, 27.21, 26.81, 26.49, 20.52, 19.83. LRMS (ESI): m/z = 434 [M + H]$^+$.
(22) Compound (*R*,*R*)-**15** (98% ee) was prepared using similar conditions to that described for the preparation of (*S*,*S*)-**15** except (*R*,*R*)-**13** (98% ee) was used in place of (*S*,*S*)-**13**.