Natural Product Synthesis

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Asymmetric Total Syntheses of Platensimycin**

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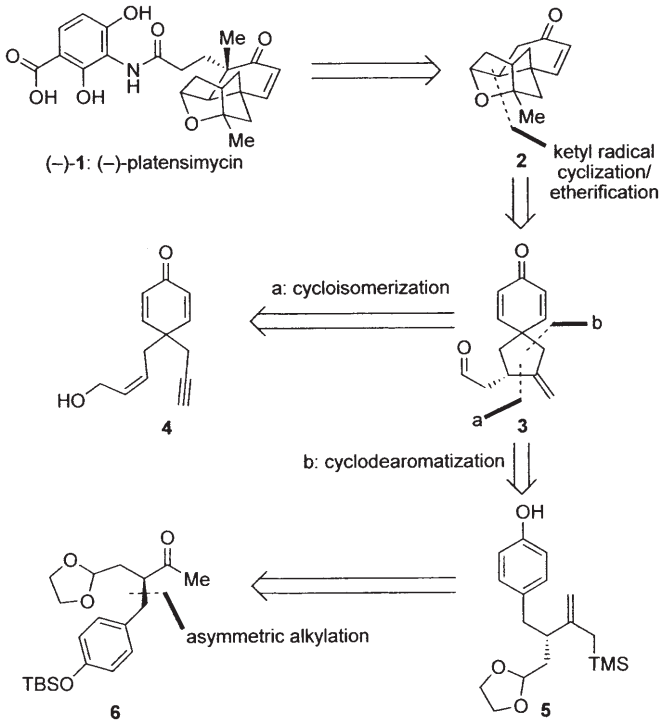
The disclosure of platensimycin ((−)-**1**, Scheme 1) and its impressive antibacterial properties[1] has generated considerable interest in the scientific and medical community. The unique mechanism of action of platensimycin, which involves the inhibition of the bacterial biosynthesis of fatty acids through the binding of platensimycin to the acyl–enzyme intermediate of the elongation-condensing enzyme β-ketoacyl-acyl carrier protein synthase I/II (FabF/B), has raised hopes for a powerful new therapy against drug-resistant bacteria. Following our recent report of the total synthesis of racemic platensimycin,[2] we now wish to describe two asymmetric total syntheses of this intriguing antibiotic.



Scheme 1. Structure and retrosynthetic analysis of (−)-**1**. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

Scheme 1 outlines the retrosynthetic analysis of (−)-**1** leading to the two successful strategies. The later stages of the asymmetric approach mirror those of our previous studies, in which the cage structure **2** is a critical intermediate target bearing all but one of the required stereogenic centers. This structure would be formed, as before, through the samarium(II) iodide-mediated cyclization of aldehyde **3**, which contains a single stereogenic center. Aldehyde **3** therefore became the focus of our planned asymmetric synthesis. The first asymmetric approach depended on the formation of **3** from enyne **4** in an enantioselective cycloisomerization process. In a conceptually different approach, **3** might also be reached by the oxidative dearomatization of a suitable phenolic precursor such as **5**, which would be available from **6**, thus allowing the installation of the requisite chiral center though an asymmetric alkylation reaction.

The planned enantioselective cycloisomerization of a substrate such as **4** is in direct analogy to our previous study[2] which exploited Trost's ruthenium(II) catalyst [CpRu(MeCN)$_3$]PF$_6$[3] (Cp = cyclopentadienyl) to form the spirocyclic framework. This reaction was not expected to be amenable to asymmetric modification, however, Zhang and co-workers reported a rhodium(I) catalyst for the asymmetric cyclization of similar substrates.[4] Enyne **4** was prepared by slight modification of our previously reported route[2] and subjected to Zhang's rhodium-catalyzed cyclization conditions,[4] however the terminal acetylene proved unsuitable with this catalyst system. The corresponding TMS-acetylene was also prepared, but failed to provide any of the desired product on exposure to the rhodium-catalyst system. This obstacle was overcome by recourse to the acetylinic ester substrate **9** (Scheme 2). Thus ester **9** was prepared from our previously reported intermediate **7**,[2] as shown. The ketone group was converted into the corresponding TMS enol ether, which allowed the introduction of the ester group through the action of *n*BuLi and Mander's reagent to give **8**. The silyl enol ether was then oxidized with IBX in the presence of MPO[5] to form the prochiral bisenone framework (67% yield over 3 steps) and acidic hydrolysis of the TBS group furnished **9** (91%). Treatment of **9** with [{Rh(cod)Cl}$_2$] and (*S*)-binap in the presence of AgSbF$_6$[4] gave the desired spirocyclic product **10** in 91% yield. Analysis of **10** by HPLC on a chiral stationary phase[6] indicated an enantiomeric excess of greater than 95% (Table 1). The stereochemistry of **10** was assigned by analogy to known examples[4] and later confirmed by

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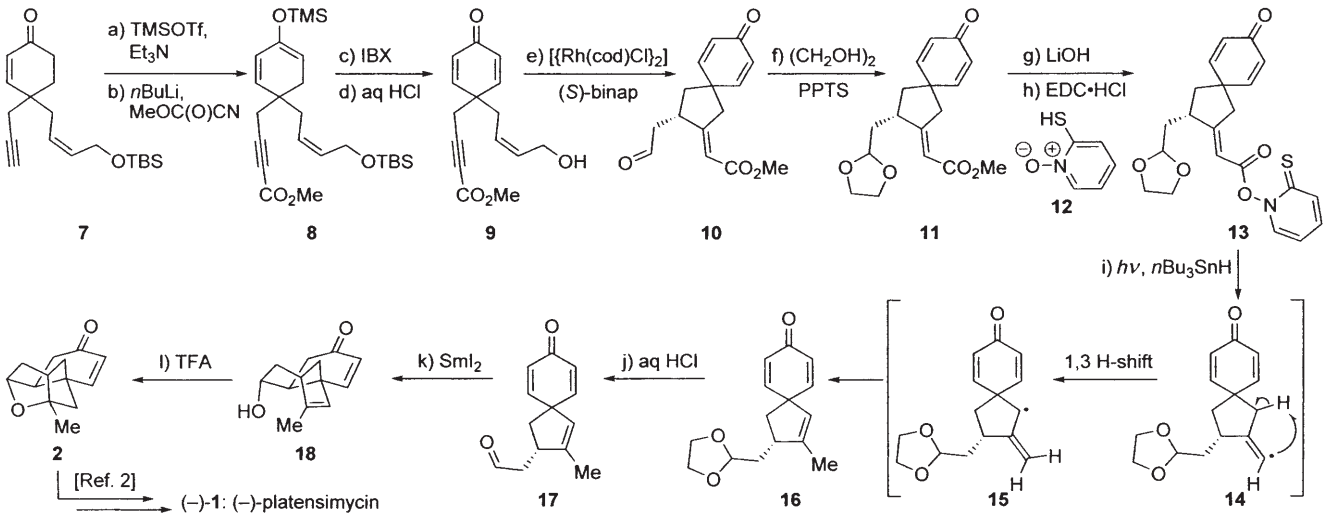
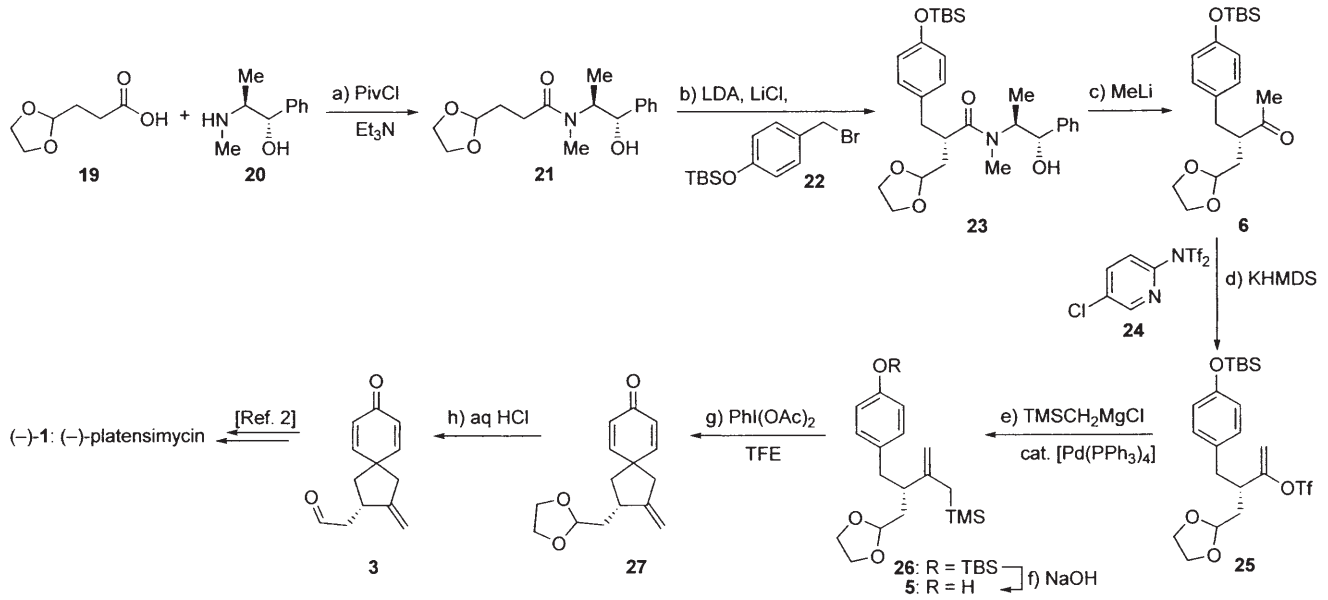


Scheme 2. Catalytic enantioselective synthesis of (−)-**1** through a rhodium-catalyzed cycloisomerization. Reagents and conditions: a) TMSOTf (1.3 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C, 10 min; b) *n*BuLi (1.39 M in hexanes, 1.2 equiv), methyl cyanoformate (1.5 equiv), THF, −78→−40 °C, 1 h; c) IBX (1.4 equiv), MPO (1.4 equiv), DMSO, 22 °C, 1 h, 67% (3 steps); d) 1 N aq HCl/THF (1:2), 0 °C, 1 h, 91%; e) $[\{Rh(cod)Cl\}_2]$ (5 mol%), (*S*)-binap (11 mol%), $AgSbF_6$ (20 mol%), DCE, 22 °C, 1.5 h, 91%; f) $(CH_2OH)_2$ (2.0 equiv), $CH(OMe)_3$ (2.0 equiv), PPTS (10 mol%), benzene, 60 °C, 3 h, 90%; g) 0.6 N aq LiOH (4.0 equiv), THF, 0 °C, 1 h; h) EDC·HCl (1.1 equiv), **12** (1.1 equiv), CH_2Cl_2, 22 °C, 2 h; i) visible light, 65 W lamp, nBu_3SnH (5.0 equiv), benzene, 22 °C, 30 min, 49% (3 steps); j) 1 N aq HCl/THF (1:1), 40 °C, 20 min, 90%; k) SmI_2 (0.1 M in THF, 2.2 equiv), HFIP (1.5 equiv), THF/HMPA (10:1), −78 °C, 1 min, 39%, l) TFA/CH_2Cl_2 (2:1), 0 °C, 1.5 h, 87%. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, DMSO = dimethyl sulfoxide, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol, HMPA = hexamethylphosphoramide, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid.

comparison of the optical rotation of **2** produced from **10** with that of material prepared from **23** (see below).

Having performed admirably in facilitating the enantioselective cycloisomerization, the carboxylate group had to be excised from the enantiomerically enriched dienone **10**. To this end, the aldehyde moiety in **10** was selectively converted into an ethylene acetal (90%) and the resulting product **11** was converted into the Barton ester[7] **13** in a two-step



Scheme 3. Chiral-auxiliary-based asymmetric synthesis of (−)-**1** through a hypervalent-iodine-mediated dearomatization. Reagents and conditions: a) **19** (1.3 equiv), PivCl (1.3 equiv), Et_3N (3.0 equiv), MeCN, 0 °C, 1 h; then **20** (1.0 equiv), Et_3N (1.0 equiv), THF, 30 min, 100%; b) LDA (2.1 equiv), LiCl (7.0 equiv), **22** (1.8 equiv), −78→0 °C, 1.5 h, 87%; c) MeLi (1.36 M in Et_2O, 4.0 equiv), THF, −78→−25 °C, 40 min, 91%; d) KHMDS (0.5 M in toluene, 2.5 equiv), **24** (2.5 equiv), THF, −78→0 °C, 1 h, 92%; e) $TMSCH_2MgCl$ (1.1 M in THF, 3.0 equiv), LiCl (3.0 equiv), $[Pd(PPh_3)_4]$ (2.5 mol%), THF, 22 °C, 30 min, 94%; f) NaOH (2.5% w/v in MeOH), 0→22 °C, 2 h, 100%; g) $PhI(OAc)_2$ (1.2 equiv), TFE, −10 °C, 20 min, 68%; h) 1 N aq HCl/THF (1:1), 40 °C, 3 h, 90%. LDA = lithium diisopropylamide, HMDS = hexamethyldisilazide, Piv = pivaloyl, TFE = 2,2,2-trifluoroethanol.

sequence that involved alkaline ester hydrolysis and coupling with 2-mercaptopyridine *N*-oxide **12**. Photolysis (visible light) of a solution of **13** and nBu$_3$SnH in benzene led to the unexpected decarboxylation product **16** (50% overall yield from **10**), in which the olefin had migrated into the ring at the position indicated in Scheme 2. This product presumably arises through a 1,3 hydrogen atom shift from the initially generated vinylic radical **14** to form the allylic radical **15**. Hydrogen atom capture from the tin hydride reagent then occurs at the less hindered primary end of the allylic system, giving the product **16**. Removal of the acetal group (90%) gave the aldehyde **17**, which was then subjected to the same cyclization conditions as used in our previous study,[2] leading to the desired secondary alcohol **18** in moderate yield (39%) as a single diastereoisomer. The excellent stereoselectivity of this reaction contrasts with that observed from the cyclization of the *exo* methylene substrate **3**[2] and reflects the subtle effects governing such processes. Gratifyingly, the endocyclic olefin **18** was found to undergo a smooth cyclization reaction to give the previously prepared intermediate **2**,[2] in enantioenriched form ($[\alpha]_D = -22.3$, $c = 0.52$, $CHCl_3$) in 87% yield.

Alongside the enantioselective catalysis approach, we also investigated an auxiliary-based asymmetric synthesis of **3** by the oxidative cyclodearomatization of a phenol bearing a pendant allylsilane group. The required chiral substrate was prepared in enantioenriched form by using Myers' asymmetric alkylation method.[8] Thus, acylation of (*S*,*S*)-pseudoephedrine (**20**) with carboxylic acid **19**[9] via the corresponding mixed anhydride (quant., Scheme 3) gave amide **21**. Alkylation of the dianion formed from **21** with the known benzylic bromide **22**[10] gave product **23** in high yield (87%) and stereoselectivity (ca. 85% *de* as indicated by ^{1}H NMR spectroscopy (500 MHz)). A single recrystallization of **23** from hexane gave essentially diastereomerically pure material. The stereochemistry of **23** was assigned by analogy to similar examples[8] and confirmed by its eventual conversion into (−)-**1**. Cleavage of the auxiliary group with MeLi (91%)[8] gave the required methyl ketone **24** with greater than 98% *ee* by HPLC,[11] reflecting the diastereomeric purity of recrystallized **23**. Ketone **24** was converted into its enol triflate using Comins' reagent (85%), and the allylsilane moiety was introduced by Kumada coupling to furnish compound **26** in 90% yield. The phenol group was then released in **26** through alkaline cleavage of the TBS group to afford the phenolic allylsilane **5** (quant.) as the substrate for the crucial dearomatization step.

The key cyclodearomatization reaction of **5** was then investigated using iodine(III) reagents.[12] A survey of the literature revealed few examples of the use of non-aromatic carbon-centered nucleophiles in oxidative dearomatizations[13,14] and an allylsilane has only been employed in a single system, in which allyltrimethylsilane was reacted in an intermolecular setting with a naphthol system.[15] Despite the lack of precedent for the involvement of allylsilane nucleophiles in such dearomatizing cyclizations, exposure of **5** to either $PhI(OAc)_2$ or $PhI(O_2CCF_3)_2$ in a variety of solvents afforded the desired spirocyclic dienone **27** in various yields. The most efficient conditions identified to date involved the use of $PhI(OAc)_2$ in trifluoroethanol at −10°C and gave dienone **27** in 68% yield. The enantiomeric excess of **27** was determined at this stage by HPLC (98% *ee*; Table 1)[16] to ensure that no racemization had occurred during the preceding sequence. Finally, removal of the ethylene acetal group under acidic conditions led to the enantiomerically enriched aldehyde **3** in 90% yield ($[\alpha]_D^{32} = -68.0$, $c = 0.60$, $CHCl_3$). This key intermediate was then converted into (−)-**1** by using the previously described route.[2] The spectroscopic properties of synthetic (−)-**1** (^{1}H and ^{13}C NMR, IR, MS) were identical to those reported previously[1b,2] and the optical rotation ($[\alpha]_D^{32} =$

Table 1: Selected physical properties for compounds **5**, **10**, **17**, and **27**.

5: $R_f = 0.40$ (silica gel, EtOAc/hexane 30:70); $[\alpha]_D^{32} = -11.3$ ($c = 0.63$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3385$br w, 2952w, 2886w, 1630w, 1614w, 1514s, 1443w, 1359w, 1247s, 1137 m, 1025w, 851s cm^{-1}; ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 7.03$–7.00 (m, 2H), 6.72–6.69 (m, 2H), 5.11 (s, 1H), 4.86 (dd, $J = 6.6$, 3.8 Hz, 1H), 4.67 (s, 2H), 3.96–3.88 (m, 2H), 3.85–3.76 (m, 2H), 2.74 (dd, $J = 13.7$, 6.0 Hz, 1H), 2.56 (dd, $J = 13.7$, 8.1 Hz, 1H), 2.42–2.36 (m, 1H), 1.78 (ddd, $J = 14.0$, 8.8, 3.8 Hz, 1H), 1.67 (ddd, $J = 13.9$, 6.5, 5.5 Hz, 1H), 1.55 (d, $J = 13.7$ Hz, 1H), 1.48 (d, $J = 13.7$ Hz, 1H), 0.37 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 153.8$, 149.3, 132.4, 130.4, 114.9, 108.1. 103.4, 64.6, 44.5, 40.1, 36.9, 25.8, −1.1 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{18}H_{29}O_3Si$ $[M+H]^+$: 321.1880; found 321.1885

10: $R_f = 0.23$ (silica gel, EtOAc/hexane 60:40); $[\alpha]_D^{20} = -51.6$ ($c = 0.45$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2951$w, 1713s, 1661s, 1623m, 1435w, 1408w, 1348w, 1259w 1210m, 1158w, 1131w, 1029w, 860m cm^{-1}; ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 9.82$ (s, 1H), 6.91 (dd, $J = 10.2$, 3.0 Hz, 1H), 6.79 (dd, $J = 10.0$, 3.0 Hz, 1H), 6.30 (dd, $J = 10.0$, 1.9 Hz, 1H), 6.24 (dd, $J = 10.1$, 1.9 Hz, 1H), 5.81 (q, $J = 2.5$ Hz, 1H), 3.71 (s, 3H), 3.49–3.42 (m, 1H), 3.23 (dt, $J = 19.1$, 2.1 Hz, 1H), 3.02 (dt, $J = 19.1$, 2.8 Hz, 1H), 2.95 (dd, $J = 18.4$, 4.6 Hz, 1H), 2.81 (ddd, $J = 19.1$, 7.8, 0.9 Hz, 1H), 2.14 (ddd, $J = 12.7$, 7.7, 2.1 Hz, 1H), 1.74 ppm (dd, $J = 12.7$, 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 199.2$, 185.6, 166.4, 153.8, 151.0, 129.2, 127.8, 114.2, 51.3, 48.2, 47.0, 43.4, 42.6, 38.3 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1121; found 261.1119

17: $R_f = 0.42$ (silica gel, EtOAc/hexane 60:40); $[\alpha]_D^{35} = +57.9$ ($c = 1.26$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2920$w, 1721m, 1661s, 1618w, 1403w, 1033w, 860m; ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 9.85$ (t, $J = 1.4$ Hz, 1H), 6.78 (dd, $J = 9.9$, 2.9 Hz, 1H), 6.72 (dd, $J = 9.8$, 2.9 Hz, 1H), 6.21 (dd, $J = 9.9$, 1.9 Hz, 1H), 6.18 (dd, $J = 9.8$, 1.9 Hz, 1H), 4.93 (s, 1H), 3.36–3.30 (m, 1H), 2.86 (ddd, $J = 17.4$, 4.6, 1.2 Hz, 1H), 2.47 (ddd, $J = 17.4$, 9.1, 1.6 Hz, 1H), 2.42 (dd, $J = 13.6$, 7.9 Hz, 1H), 1.77 (a, 3H), 1.76 ppm (dd, $J = 13.4$, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.7$, 185.6, 154.2, 152.8, 146.5, 128.0, 127.2, 126.6, 53.2, 48.2, 42.2, 41.9, 15.0; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067; found 203.1060

27: $R_f = 0.42$ (silica gel, EtOAc/hexane 60:40); $[\alpha]_D^{33} = -57.9$ ($c = 0.44$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2950$w, 2883w, 1659s, 1623m, 1430w, 1407m, 1259m, 1135m, 1091m, 1021m, 916m, 858s, 730m, 705m; ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 6.97$ (dd, $J = 10.1$, 3.0 Hz, 1H), 6.80 (dd, $J = 9.9$, 3.0 Hz, 1H), 6.25 (dd, $J = 9.9$, 1.9 Hz, 1H), 6.22 (dd, $J = 10.1$, 1.9 Hz, 1H), 5.08–5.07 (m, 1H), 5.03–5.01 (m, 1H), 4.91 (dd, $J = 5.1$, 4.4 Hz, 1H), 4.00–3.95 (m, 2H), 3.88–3.83 (m, 2H), 2.99–2.91 (m, 1H), 2. 64 (dq, $J = 15.9$, 2.4 Hz, 1H), 2.44 (dd, $J = 15.9$, 1.6 Hz, 1H), 2.14 (ddd, $J = 14.0$, 5.2, 4.2 Hz, 1H), 2.08 (ddd, $J = 13.0$, 7.9, 1.7 Hz, 1H), 1.80 (dd, $J = 13.0$, 10.4 Hz, 1H), 1.76 ppm (ddd, $J = 14.0$, 10.1, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 186.1$, 155.0, 152.7, 152.2, 128.5, 127.4, 108.1, 103.3, 64.9, 64.7, 47.0, 44.3, 44.3, 39.2, 38.0 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329; found 247.1321

−43.7, $c = 0.30$, MeOH) was in agreement with that reported for the natural material ($[\alpha]_D^{23} = -51.1$, $c = 0.135$, MeOH).[1b]

In addition to demonstrating the power of modern asymmetric synthesis, the reported enantioselective syntheses of platensimycin [(−)-**1**] may prove useful in rendering this new antibiotic and its analogues readily available for further biological and pharmacological studies.

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[16] HPLC conditions: Chiracel OD-H, hexane/*i*PrOH 90:10, 0.1 mL min^{-1}, $R_{t(minor)} = 15.89$ min, $R_{t(major)} = 18.05$ min; racemic **27** was prepared from racemic **3**[2] by using the method described for the preparation of **11** from **10**.

