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Catalytic enantioselective synthesis of a novel inhibitor of ceramide trafficking, (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)-dodecanamide (HPA-12)

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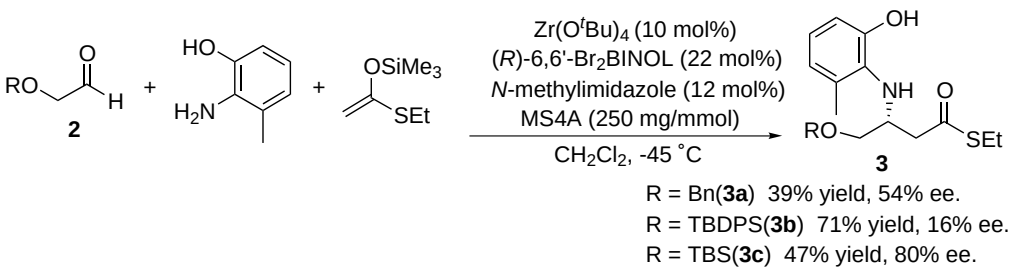
Abstract—A novel inhibitor of ceramide trafficking, (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12), has been synthesized using a chiral zirconium-catalyzed asymmetric Mannich-type reaction as a key-step.

Sphingolipid biosynthesis is now of great interest because of its important roles in cell growth, differentiation, and apotosis, etc.[1] Enzymes that catalyze sphingolipid biosynthesis are targets for chemists as well as biologists to create new drugs. Our group has accomplished total synthesis of sphingofungin B,[2] an inhibitor of serinepalmitoyl transferase (SPT), and more recently, khafrefungin,[3] an inhibitor of inositol phosphorylceramide (IPC), and the structural relationship of biological activity has been clarified. In the course of our investigations to search for a new molecule that shows a characteristic property in sphingolipid biosynthesis, we have found that (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12, **1**) is a novel inhibitor of ceramide trafficking from endoplasmic reticulum to the site of sphingomyelin (SM) synthesis. HPA-12 is the first compound of the specific inhibitor for SM synthesis in mammalian cells, and a potential drug that inhibits intracellular trafficking of sphingolipids.[4] In this report, we describe the first synthesis of HPA-12 using a chiral zirconium-catalyzed enantioselective Mannich reaction as a key-step.



Scheme 1.

Keywords: HPA-12; a novel inhibitor of ceramide trafficking; Mannich-type reaction; asymmetric reaction.
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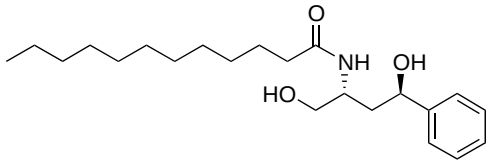
In the initial and key-step, we examined the three-component reaction of an α-alkoxy aldehyde, 2-amino-*m*-cresol, and 1-ethylthio-1-trimethylsiloxyethene in the presence of a catalytic amount of a chiral zirconium complex prepared from zirconium *tert*-butoxide, (*R*)-6,6′-Br_2BINOL, and *N*-methylimidazole(Scheme 1).[5] It was found that the alkoxy part of the aldehyde significantly influenced the enantioselectivity of the product, and that a high level of selectivity was obtained when the *tert*-butyldimethylsiloxy group was used. The benzyloxy group and more bulky *tert*-butyldiphenylsiloxy group gave much lower selectivity.

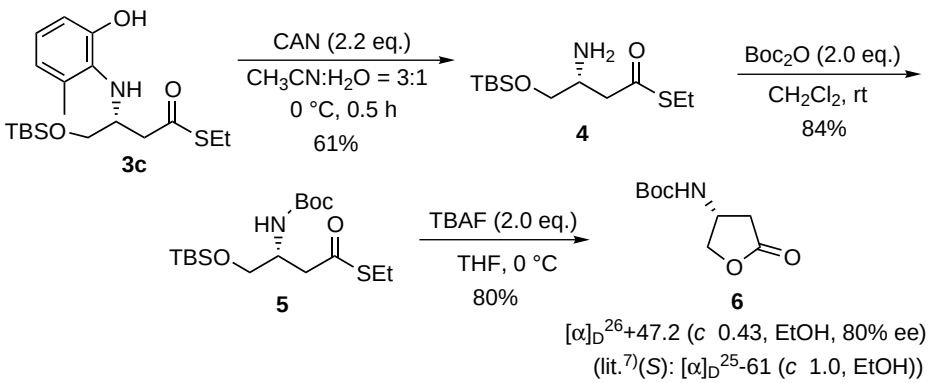


(1*R*,3*R*)-HPA-12 **(1)**

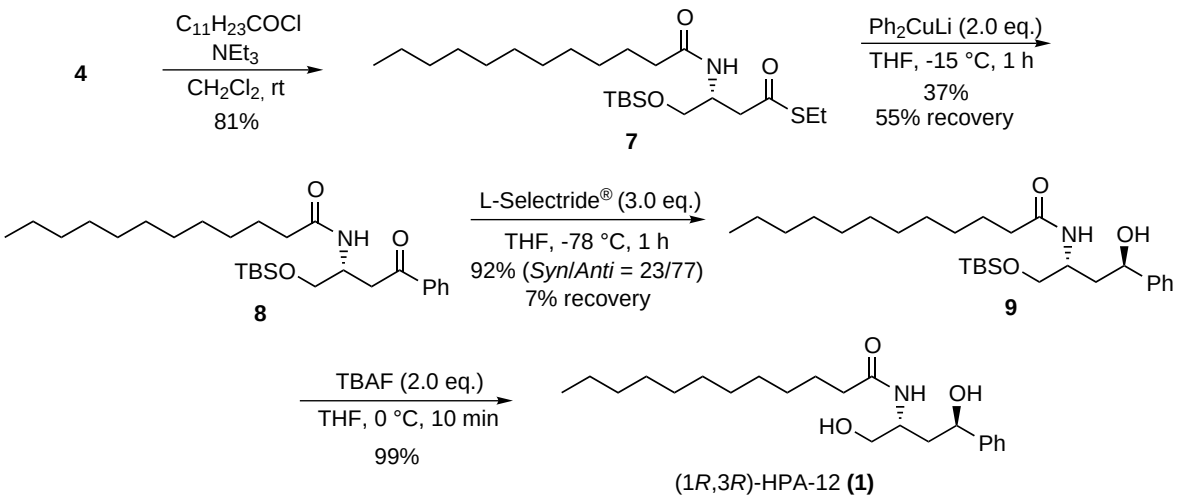
The absolute configuration of the product **3c**[6] was determined after converting to literature-known lactone **6** as shown in Scheme 2. Treatment of **3c** with cerium ammoniumnitrate (CAN) in acetonitrile–water (3:1) gave amine-free adduct **4** in 61% yield. *t*-Butoxycarbonyl (Boc) protection of the amino group followed by deprotection of the *t*-butyldimethylsiloxy group gave the desired lactone **6** in high yield. Comparison of the optical rotation of **6** with that in literature[7] revealed that the absolute configuration of Mannich adduct **3c** was *R*.

The preparation of HPA-12 from **3c** was performed according to the transformations shown in Scheme 3. The adduct **4** was acylated under standard conditions to give amide **7** in 81% yield. Conversion of **7** to ketone **8** was performed using diphenylcopper lithium in THF at −15°C for 1 h. While the yield of **8** was moderate (37%), 55% of the starting material (**7**) was recovered (82% conversion yield). Anti-selective reduction of **8** proceeded using L-Selectride® in THF at −78°C (92%, *syn*/*anti*=23/77).[8] The use of lithium borohydride instead of L-Selectride® gave lower selectivity (82%, *syn*/*anti*=54/46). These selectivity would be explained by the preferential conformation of **8**.[9] Finally, deprotection of the *tert*-butyldimethylsiloxy group of **9** using tetrabutylammonium fluoride gave HPA-12 in 99% yield. After recrystallization from ether/hexane, HPA-12 was obtained in 96% ee.[10]

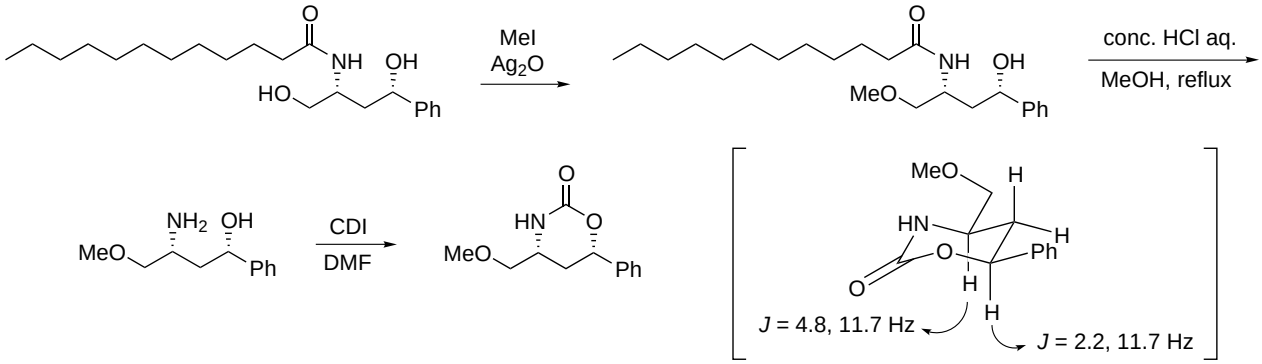
Thus, HPA-12, a novel inhibitor of ceramide trafficking, has been synthesized using a chiral zirconium-catalyzed Mannich-type reaction as a key-step. Based on



Scheme 2.



Scheme 3.



Scheme 4.

this synthetic scheme, we have synthesized all four stereoisomers of HPA-12, and confirmed that only the (1*R*,3*R*)-isomer showed high activity.[4] Further investigations to search for more active compounds as well as to clarify biological aspects of the inhibition are now in progress.

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6. **Compound 3c**: $[\alpha]_D^{21}$ +8.26 (*c* 1.23, $CHCl_3$, 80% ee); IR (neat): 3358, 2928, 2856, 1680, 1589, 1476, 1254, 836 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.85 (s, 9H), 1.18 (t, 3H, $J=7.4$ Hz), 2.18 (s, 3H), 2.66 (dd, 1H, $J=4.7$, 13.9 Hz), 2.82 (q, 2H, $J=7.5$ Hz), 2.85 (m, 1H), 3.40 (dd, 1H, $J=3.6$, 8.2 Hz), 3.45–3.56 (m, 2H), 6.56 (dd, 1H, $J=0.7$, 7.2 Hz), 6.68 (dd, 1H, $J=1.3$, 7.2 Hz), 6.79 (t, 1H, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$): δ −5.6, −5.5, 14.6, 17.6, 18.3, 23.6, 25.9, 46.1, 55.7, 64.0, 113.5, 121.6, 124.8, 131.5, 132.4, 152.1, 199.7; HPLC: Daicel Chiralpak AD, hexane/^{i}PrOH = 200/1, flow rate = 1.0 ml/min: ^{t}R = 16.5 min (3*R*), ^{t}R = 20.3 min (3*S*); HRMS: calcd for $C_{19}H_{33}NO_3SSi$ (M^+) 383.1950, found 383.1932.
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10. **HPA-12** (**1**): mp 75.5–77.0°C; $[\alpha]_D^{22}$ −35.1 (*c* 0.8, $CHCl_3$, 96% ee); IR (neat): 3293, 2919, 2849, 1643, 1551, 1493, 1054, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, $J=6.8$ Hz), 1.26 (bs, 16H), 1.59 (bt, 2H, $J=7.2$ Hz), 1.92 (ddd, 1H, $J=6.6$, 8.5, 15.1 Hz), 2.03 (ddd, 1H, $J=3.6$, 5.7, 14.6 Hz), 2.15 (t, 2H, $J=7.7$ Hz), 3.65 (ddd, 1H, $J=4.1$, 11.3, 15.5 Hz), 4.01–4.08 (m, 1H), 4.79 (dd, 1H, $J=3.4$, 8.8 Hz), 6.48 (d, 1H, $J=6.8$ Hz), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.7, 29.3, 29.3, 29.3, 29.5, 29.6, 29.6, 31.9, 36.8, 40.7, 50.4, 65.5, 71.8, 125.5, 127.7, 128.5, 144.2, 174.3; HPLC: Daicel Chiralpak AD, hexane/^{i}PrOH = 19/1, flow rate = 1.0 ml/min: ^{t}R = 11.4 min (1*S*,3*S*), ^{t}R = 15.0 min (1*R*,3*R*); HRMS: calcd for $C_{22}H_{37}NO_3$ (M^+) 363.2273, found 363.2279.