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Catalytic Asymmetric Synthesis of Both *syn*- and *anti*-3,5-Dihydroxy Esters: Application to 1,3-Polyol/α-Pyrone Natural Product Synthesis

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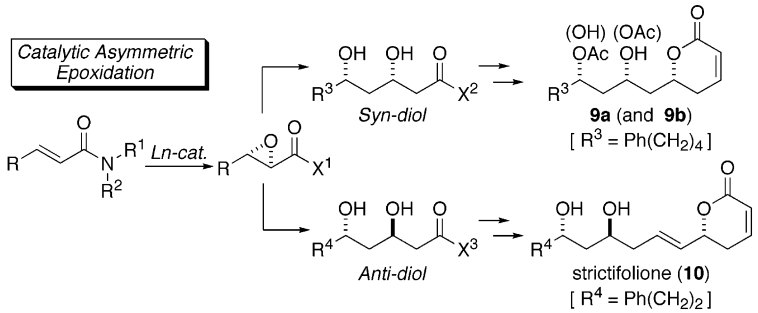
ABSTRACT



We describe a catalytic asymmetric synthesis of both *syn*- and *anti*-3,5-dihydroxy esters. The method relies upon catalytic asymmetric epoxidation of α,β-unsaturated imidazolides and amides, using lanthanide-BINOL complexes, and diastereoselective reduction of ketones. The method was applied to the enantioselective syntheses of 1,3-polyol/α-pyrone natural products 9a, 9b, and strictifolione (10). The absolute stereochemistry of 9a and 9b was also determined.

Optically active *syn*- and *anti*-1,3-diol units are ubiquitous structural motifs in various biologically active compounds. For example, the polyene class of macrolide antibiotics contains extended 1,3-polyol chains as the common structural feature.[1] Due to their distribution, as well as their interesting structure, extensive efforts have focused on the development of an efficient synthetic method for stereoselective construction of these core fragments.[1,2] Among the many methods reported to date, Leighton's tandem reaction strategy is the state of the art in this field, affording *syn*,*syn*-1,3,5-triols diastereoselectively in a single-pot reaction.[3,4] In addition, efficient approaches to optically active 1,3-diol units have been achieved by using several catalytic asymmetric reactions.[5−8] We recently developed the catalytic asymmetric epoxidation of α,β-unsaturated imidazolides[9c] and α,β-unsaturated amides[9d] using a lanthanide-BINOL (Ln-BINOL)

(1) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.
(2) For a review, see: Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375.
(3) (a) Zucuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587 and references therein. (b) Wang, X.; Meng, Q.; Nation, A. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672. (c) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890.
(4) For the one-pot, five-component linchpin coupling tactic, see: Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001.
(5) Noyori hydrogenation: (a) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058. (b) Sinz, C. J.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3224.
(6) Sharpless asymmetric epoxidation: (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Vitti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (b) Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1998**, 109.
(7) Sharpless asymmetric dihydroxylation: (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049. (b) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777.
(8) Biocatalytic reduction: Wolberg, M.; Hummel, W.; Müller, M. *Chem. Eur. J.* **2001**, *7*, 4562.
(9) (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai. H.; Shibasaki. M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725 and references therein. (c) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474. (d) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544.

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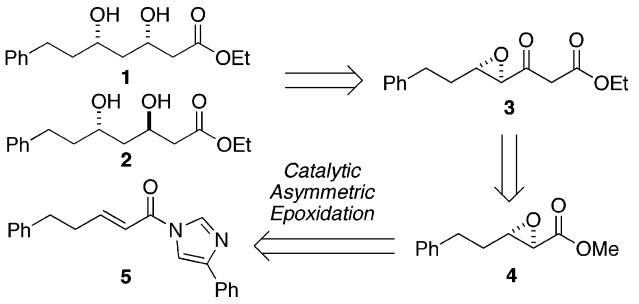
complex.[9] The present catalytic asymmetric synthesis of *syn*- and *anti*-1,3-diol units is an extension of these catalytic asymmetric reactions. Herein, we report an efficient enantioselective synthesis of both *syn*- and *anti*-3,5-dihydroxy ester units using catalytic asymmetric epoxidation. We also describe the enantioselective syntheses of 1,3-polyol/α-pyrone natural products using this method.

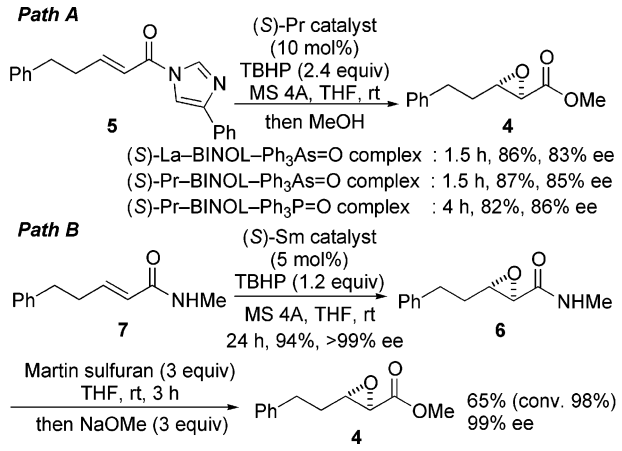
Scheme 1



Our initial strategy is outlined in Scheme 1. Both *syn*- and *anti*-3,5-dihydroxy esters **1** and **2** were expected to be obtained by reductive epoxide opening of γ,δ-epoxy β-keto ester **3**, followed by diastereoselective reduction. The common intermediate **3** should be synthesized from the corresponding α,β-epoxy ester **4**, which is produced by the catalytic asymmetric epoxidation of α,β-unsaturated imidazolide **5**.

Synthetic studies began with a detailed optimization of a catalytic asymmetric epoxidation of **5** (Scheme 2, Path A).[10]

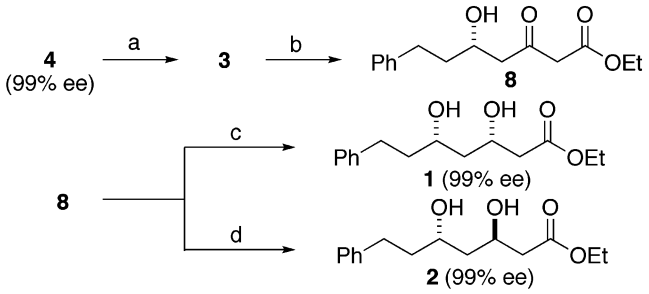
Scheme 2



First, the effect of the central metal was investigated by using 10 mol % of (*S*)-Ln−BINOL−Ph_3As=O complex, generated from Ln(O-*i*-Pr)$_3$, (*S*)-BINOL, and Ph_3As=O in a ratio of 1:1:1. The (*S*)-Pr−BINOL−Ph_3As=O (1:1:1) complex functioned best for this reaction, affording **4** in 87% yield and in 85% ee. Moreover, there was a slight improvement in the enantioselectivity when using the (*S*)-Pr−BINOL−Ph_3P=O (1:1:3) complex (82%, 86% ee).[11] Due to the difficulty of enantioenrichment by recrystallization, an alternative method was explored. Very recently, a highly enantioselective epoxidation of α,β-unsaturated amides with Sm−BINOL−Ph_3As=O (1:1:1) complex was achieved.[9d] To apply this catalytic asymmetric reaction, we focused on the development of an efficient conversion of α,β-epoxy amide **6** to **4** (Scheme 2: Path B). With 5 mol % of (*S*)-Sm−BINOL−Ph_3As=O (1:1:1) complex, epoxidation of α,β-unsaturated amide **7** proceeded smoothly to provide optically pure **6** in 94% yield. After several attempts, treatment of **6** with Martin sulfurane,[12] followed by the addition of sodium methoxide afforded **4** (65%, conv. 98%) without any noticeable loss of optical purity.

Having obtained nearly optically pure **4**, further transformations were examined (Scheme 3). The lithium enolate of ethyl acetate was reacted with **4** at low temperature, giving γ,δ-epoxy β-keto ester **3** in 87% yield. Extensive investigation[10] of the reductive epoxide opening reaction indicated that a selenium reagent, prepared from PhSeSePh and $NaBH_4$ in EtOH, was very effective in the reaction, affording δ-hydroxy β-keto ester **8** in 85% yield.[13] Finally, both syn-selective[14] and anti-selective[15] reductions of **8** were performed, using the known methods. The corresponding *syn*-3,5-dihydroxy ester **1** and *anti*-3,5-dihydroxy ester **2** were obtained in 79% isolated yield (syn:anti >20:1) and in 80% isolated yield (syn:anti 1:9), respectively. The enantiomeric excesses of both diastereomers were determined after conversion of the diols into acetonides, and no racemization occurred during the process.[16] Enantiomers of both **1** and **2**

Scheme 3 [a]



[a] Conditions: (a) ethyl acetate, LHMDS, THF, −78 to −20 °C, 87%. (b) PhSeSePh, $NaBH_4$, EtOH, rt, 85%; (c) BEt_2(OMe), $NaBH_4$, THF-MeOH, −78 °C, 79%; (d) $NMe_4BH(OAc)_3$, CH_3CN-AcOH, 0 °C, 80%.

(10) For detailed data, see the Supporting Information.

(11) Daikai, K.; Kamaura, M.; Inanaga, J. *Tetrahedron Lett.* **1998**, *39*, 7321.
(12) Martin, J. C.; Franz, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 6137.
(13) Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* **1988**, 507.
(14) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(15) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

are available, using the catalyst with the opposite enantiomer of BINOL.

Having established efficient routes to both *syn*- and *anti*-3,5-dihydroxy esters, we applied the developed methods to the enantioselective syntheses of 1,3-polyol/α-pyrone natural products **9a**, **9b**, and strictifolione (**10**) (Figure 1).

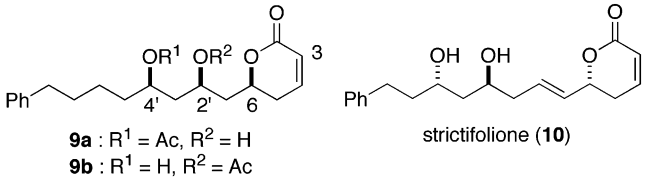
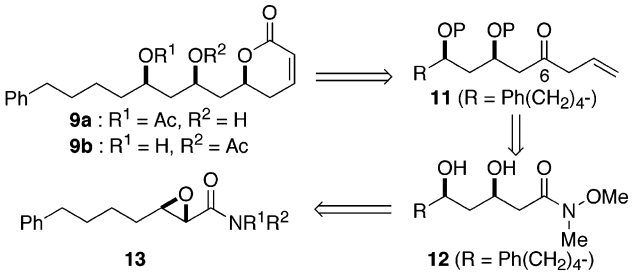


Figure 1. 1,3-Polyol/α-pyrone natural products **9a**, **9b**, and strictifolione (**10**).

Compounds **9a** and **9b**, isolated from the leaves and bark extract of *Ravensara anisata*, exhibit antifungal activity.[17] Structural analysis of **9** revealed that the three oxygenated chiral centers have syn,syn relative stereochemical relationships. The retrosynthetic analysis of **9** is shown in Scheme 4. We planned to introduce the C(6) stereocenter of **9** using

Scheme 4



a diastereoselective reduction of ketone **11**, which was expected to be obtained from *syn*-3,5-dihydroxy amide **12**. **12** should be synthesized from α,*β*-epoxy amide **13**, using the method described above.

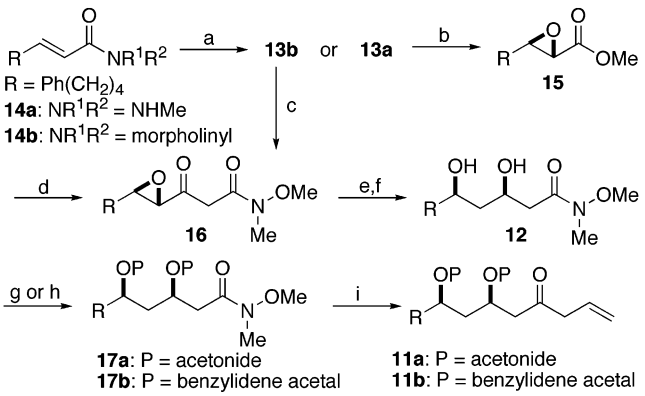
The initial stage of the synthesis is shown in Scheme 5. Catalytic asymmetric epoxidation of **14a** with 10 mol % of the (*R*)-Sm catalyst proceeded smoothly, yielding α,*β*-epoxy amide **13a** in 87% yield and in 99% ee.[18] After conversion of **13a** into the corresponding methyl ester **15** (71%, conv. 97%), **15** was then treated with the lithium enolate prepared from *N*-methoxy *N*-methyl acetoamide. As a result, the desired *γ*,*δ*-epoxy *β*-keto amide **16** was obtained in 89% yield. Furthermore, we were pleased to find that catalytic asymmetric epoxidation of morpholinyl amide **14b**, using

(16) Enantiomeric excesses were determined by HPLC analysis.

(17) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoecki-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265.

(18) The absolute configuration was determined by Mosher's method after conversion to the corresponding *β*-hydroxy methyl ester.

Scheme 5 [a]

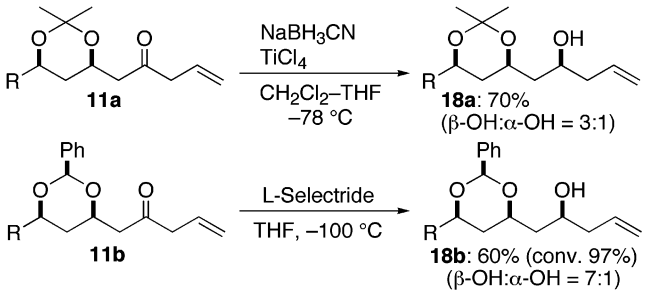


[a] Conditions: (a) catalytic asymmetric epoxidation; (b) Martin sulfurane, THF, rt, then NaOMe, 71% (conv. 97%); (c) MeCON(OMe)Me, LHMDS, THF, −78 to −50 °C, 60% (conv. 85%); (d) MeCON(OMe)Me, LHMDS, THF, −78 to −30 °C, 89%; (e) PhSeSePh, $NaBH_4$, EtOH, rt, 84%; (f) $BEt_2(OMe)$, $NaBH_4$, THF-MeOH, −78 °C; (g) dimethoxypropane, TsOH (cat.), DMF, rt, 76% (2 steps); (h) $PhCH(OMe)_2$, PPTS (cat.), toluene, reflux, 74% (2 steps); (i) AllylMgBr, THF, 0 °C, **11a** 84%, **11b** 87%

10 mol % of the (*R*)-Sm catalyst (92%, >99% ee), followed by treatment with the corresponding lithium enolate, gave **16** in one fewer step (60%, conv. 85%).[19] After a reductive epoxide opening reaction of **16** (84%), syn-selective reduction was performed to give the desired *syn*-3,5-dihydroxy amide **12** exclusively. The diol moiety was then converted into an acetonide or benzylidene acetal, affording the protected amides **17a** (76% for 2 steps) and **17b**[16] (74% for 2 steps), respectively. Treatment of **17a** and **17b** with allylmagnesium bromide resulted in successful conversion into the corresponding *β*,*γ*-unsaturated ketone **11a** (84%) and **11b** (87%), without double bond isomerization.

The key diastereoselective reduction was then studied (Scheme 6).[10] Although various studies with **11a** were

Scheme 6



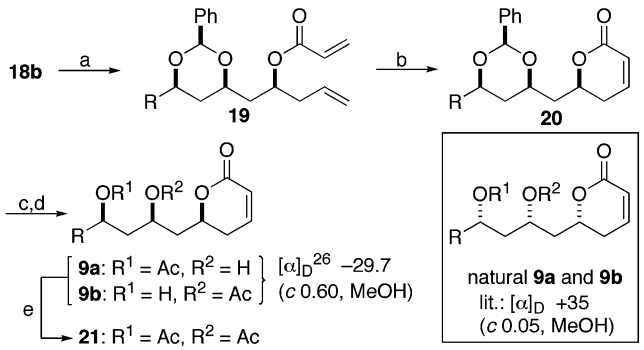
performed, the desired alcohol **18a** was obtained with modest selectivity (up to 3:1 ratio). Diastereoselective reduction, however, with **11b** proceeded with higher selectivity. After several attempts, the desired alcohol **18b** was obtained in

(19) Martín, R.; Romea, P.; Urpí, T. F.; Vilarrasa, J. *Synlett* **1997**, 1414.

good conversion (60%, conv. 97%) and with reasonable selectivity (7:1 ratio) when L-Selectride was used at −100 °C.[20]

Having succeeded in the synthesis of **18b**, the stage was set for the completion of the total synthesis (Scheme 7). After

Scheme 7 [a]

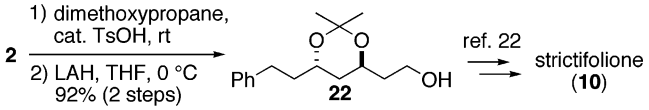


[a] Conditions: (a) acryloyl chloride, *i*-Pr_2NEt, CH_2Cl_2, rt, 91%; (b) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (4 mol %), CH_2Cl_2, reflux, 84%; (c) 80% aq. AcOH, 60 °C; (d) $MeC(OEt)_3$, PPTS (cat.), CH_2Cl_2, rt; then H_2O, 76% (2 steps); (e) Ac_2O, DMAP (cat.), pyridine, rt, 89%.

the formation of acryloyl ester **19** (91%), the 5,6-dihydro-α-pyrone ring was constructed by ring-closing metathesis.[21] In the presence of 4 mol % of Grubbs's catalyst, lactone **20** was obtained in 84% yield. In this stage, two diastereomers of **20** were separated, and the major isomer was utilized for the final conversion. Finally, removal of the benzylidene group, followed by monoacetylation of the resulting crude diol via cyclic ortho ester formation yielded **9a** and **9b** in good yield (76% for 2 steps). Diacetate **21** was also obtained from **9a** and **9b**. Spectral data of **9a**, **9b**, and **21** were identical with those reported in the literature (^1H and ^{13}C NMR spectra).[17] The optical rotation of synthetic **9a** and **9b** ($[\alpha]_D^{26}$ −29.7 (*c* 0.60, MeOH)) was opposite to the reported one ($[\alpha]_D$ +35 (*c* 0.05, MeOH)).[10] These results indicated that the absolute stereochemistry of natural products was 6*S*,4′*S*,2′*R*.

In addition, *anti*-3,5-dihydroxy ester **2** was easily converted into the intermediate for use in Aimi's total synthesis of **10** (Scheme 8).[22] Transformation of the diol into an acetonide

Scheme 8



followed by reduction of the ester afforded the known intermediate **22** (92% for 2 steps). This can be utilized for catalytic asymmetric synthesis of **10**.

In conclusion, we developed an efficient enantioselective synthesis of both *syn*- and *anti*-3,5-dihydroxy ester units using catalytic asymmetric epoxidation. In addition, the developed method was applied to the enantioselective total syntheses of 1,3-polyol/α-pyrone natural products **9a**, **9b**, and strictifolione (**10**). Further applications are under investigation in our group.

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Supporting Information Available: Experimental procedures and characterization of the products; other detailed results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Stereoselective reduction of *β*-alkoxy ketones, see: ref 7b and: Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423.

(21) For representative reviews on ring-closing methathesis, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(22) Juliawaty, L. D.; Watanabe, Y.; Kitajima, M.; Achmad, S. A.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8657 and references therein.