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Asymmetric synthesis of (−)-acaterin☆

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Abstract—The asymmetric synthesis of (−)-acaterin, an inhibitor of acyl-CoA cholesterol acyl transferase has been achieved starting from the commercially available starting materials, octan-1-ol and methyl (*R*)-lactate. The key steps are a Sharpless asymmetric dihydroxylation and a Wittig olefination.

Acyl-CoA cholesterol acyl transferase (ACAT) plays an important role in cholesterol ester accumulation in atherogenesis[1] and in cholesterol absorption from the intestines.[2] Inhibitors of ACAT activity are expected to be effective for the treatment of atherosclerosis and hypercholesterolemia. Acaterin (Fig. 1) is one of the ACAT inhibitors isolated from a culture broth of *Pseudomonas* sp. A92 by Endo and co-workers.[3] Acaterin has a butenolide skeleton with an alkyl chain at the C-2 position, which is related to Annonaceous acetogenins,[4] and has remarkable antitumor activity.[3] While Kitahara and co-workers[5] established the absolute stereochemistry after the synthesis of all the diastereomers of acaterin, the biosynthesis of acaterin was investigated by Fujimoto.[6] Synthetic strategies based on the Baylis–Hillman reaction have recently been reported for this molecule simultaneously by two different research groups.[7] As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones[8] and amino alcohols,[9] we became interested in developing a simple and feasible route to acaterin. In this paper we report a concise synthesis of (−)-acaterin employing the Sharpless asymmetric dihydroxylation procedure and a Wittig olefination as key steps.

The synthesis of (−)-acaterin started from commercially available octan-1-ol **4** as illustrated in Scheme 1. Compound **4** was oxidized to the aldehyde and subsequently treated with (methoxycarbonylmethylene)triphenylphosphorane in THF under reflux to give the Wittig product **5** in 93% yield. The dihydroxylation of olefin **5** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ as chiral

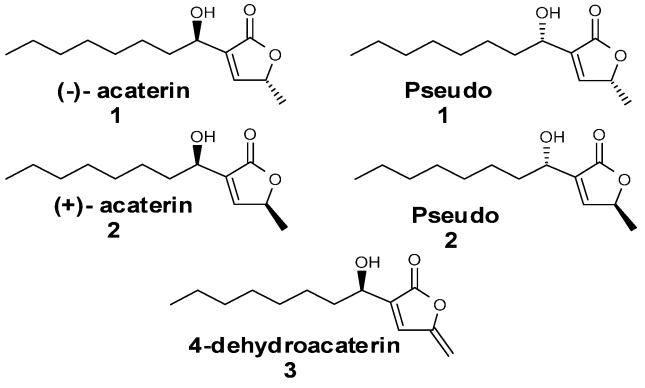
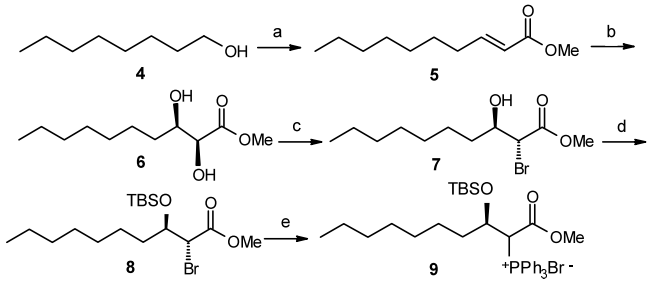


Figure 1.



Scheme 1. *Reagents and conditions*: (a) (i) P_2O_5, DMSO, CH_2Cl_2, Et_3N, 0°C, 4 h, 96%; (ii) $Ph_3P{=}CHCOOMe$, THF, reflux, 12 h, 93%; (b) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0°C, 98%; (c) HBr/AcOH, dry MeOH, 40°C, 24 h, 83%; (d) TBDMSCl, imidazole, DMAP (cat.), CH_2Cl_2, 36 h, 92%; (e) PPh_3, CH_3CN, reflux, 12 h, 66%.

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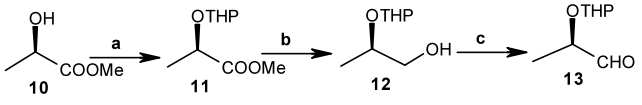
ligand under the Sharpless asymmetric dihydroxylation conditions[10] gave the diol **6** in excellent yield, $[\alpha]_D^{25}$ +11.23 (*c* 1, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$ +10.1 (*c* 1.42, $CHCl_3$)]. Regioselective conversion of the diol **6** to bromohydrin **7** was achieved employing the protocol developed by Sharpless.[12] Thus, treatment of **6** with hydrogen bromide in acetic acid gave **7**[13] in 83% yield. Subsequently, the hydroxyl group was protected as a silyl ether using *tert*-butyldimethylsilyl chloride and imidazole in the presence of a catalytic amount of DMAP to afford **8** in 92% yield which on treatment with triphenylphosphine in acetonitrile under reflux conditions furnished the phosphonium salt **9** in good yield.

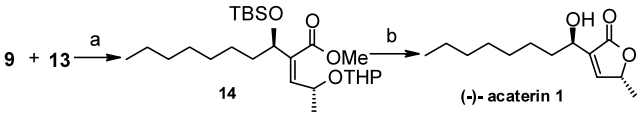
Scheme 2 summarizes the preparation of fragment **13** from the commercially available methyl (*R*)-lactate. Hydroxyl protection of **10** as the THP ether was followed by reduction of the ester to the corresponding alcohol **12** in good yield. The subsequent PCC oxidation resulted in the formation of the aldehyde **13**, which was used in the next reaction without any further purification.

The final step involved the coupling of phosphonium salt **9** with aldehyde **13** and subsequent cyclization. To this end, the Wittig olefination between **9** and **13** was carried out in the presence of LiHMDS at −78°C to give the olefin **14**[14] in 73% yield. Subsequent cyclization using a catalytic amount of *p*-TsOH in methanol furnished (−)-acaterin in 68% yield, $[\alpha]_D^{25}$ −21.33 (*c* 0.3, $CHCl_3$) [lit.[5] $[\alpha]_D^{25}$ −19.7 (*c* 0.61, $CHCl_3$)] (Scheme 3). The physical and spectroscopic data of **1** were in full agreement with the literature data.[5]

In conclusion, we have developed a new synthetic route to (−)-acaterin employing Sharpless asymmetric dihydroxylation and Wittig olefination as key steps. A short reaction sequence and high yielding steps to (−)-acaterin renders our strategy a good alternative to the known methods. Currently, studies are in progress for the synthesis of other isomers of acaterin including 4-dehydroacaterin, using an intermolecular Reformatsky reaction as the key step.



Scheme 2. *Reagents and conditions*: (a) DHP, *p*-TsOH (cat.), dry CH_2Cl_2, 96%; (b) $LiAlH_4$, dry THF, 0°C–rt, 12 h, 92%; (c) PCC, anhydrous CH_3COONa, Celite, 4 h.



Scheme 3. *Reagents and conditions*: (a) LiHMDS, dry THF, −78°C, 30 min then **13**, 10 h, 73%; (b) cat. *p*-TsOH, MeOH, overnight, 68%.

Acknowledgements

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References

1. Bell, F. P. In *Pharmacological Control of Hyperlipidemia*; Prous, J. R., Ed.; Science Publishers, 1986; pp. 409–422.
2. Heilder, J. G. In *Pharmacological Control of Hyperlipidemia*; Prous, J. R., Ed.; Science Publishers, 1986; pp. 423–438.
3. Naganuma, S.; Sakai, K.; Endo, A. *J. Antibiot*. **1992**, *45*, 1216–1221.
4. (a) Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. *J. Cancer Chemother. Rep*. **1972**, *3*, 1–88; (b) Rupprecht, J. K.; Hui, Y. H.; McLaughlin, J. L. *J. Nat. Prod*. **1990**, *53*, 237–278; (c) Fang, X. P.; Rieser, M. J.; Gu, Z. M.; Zhao, G. X.; McLaughlin, J. L. *Phytochem. Anal*. **1993**, *4*, 27–48.
5. Ishigami, K.; Kitahara, T. *Tetrahedron* **1995**, *51*, 6431–6442.
6. Sekiyama, Y.; Fujimoto, Y.; Hasumi, K.; Endo, A. *J. Org. Chem*. **2001**, *66*, 5649–5654.
7. (a) Vijay Anad, R.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett*. **2002**, *43*, 5393–5395; (b) Franck, X.; Figadere, B. *Tetrahedron Lett*. **2002**, *43*, 1449–1451.
8. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445–13450; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349–4356; (c) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem*. **2002**, 2921–2923.
9. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem*. **2000**, 3447–3449; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2000**, *41*, 10309–10312; (c) Kandula, S. R. V.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1957–1958; (d) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2002**, *43*, 4425–4426; (e) Fernandes, R. A.; Kumar, P. *Synthesis* **2003**, 129–135; (f) Naidu, S. V.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1035–1037.
10. (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **1996**, *35*, 448–481; (b) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem*. **1996**, *61*, 3055–3060; (c) for a review on asymmetric dihydroxylation, see: Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483–2547.
11. Gurjar, M. K.; Sylesh Kumar, V.; Venkateswara Rao, B. *Tetrahedron* **1999**, *55*, 12563–12576.
12. Fleming, R. P.; Sharpless, K. B. *J. Org. Chem*. **1991**, *56*, 2869–2875.
13. **Compound 7**: $[\alpha]_D^{25}$ +36.14, mp 41–41.5°C, IR ($CHCl_3$): 3604, 3019, 2928, 2400, 1735, 1658, 1215, 756, 669; ^1H NMR (200 MHz): 0.85 (t, $J=6.3$ Hz, 3H), 1.26–1.42 (m, 10H), 1.81–1.92 (2H, m), 3.01 (bs, 1H), 3.77 (s, 3H), 4.09–4.13 (d, $J=8$ Hz, 1H), 3.97 (m, 1H); ^{13}C NMR (50 MHz): 13.81, 22.41, 25.02, 28.96, 29.14, 31.57, 33.22, 47.89, 52.74, 72.11, 169.70; MS: *m*/*z* 279 (M^+−2), 263, 197, 183, 168, 152, 140, 123, 111, 95, 81. Anal. calcd for $C_{11}H_{21}O_3Br$ (281.18) C, 46.98; H, 7.52; Br, 28.41. Found C, 47.07; H, 7.65; Br, 28.14%.

14. **Compound 14**: $[\alpha]_D^{25}$ −12.67, IR (neat): 1723, 1666; ^{1}H NMR (500 MHz): 0.03 (s, 3H), 0.08 (s, 3H), 0.86–0.89 (t, $J=6.3$ Hz, 3H), 1.28–1.31 (m, 10H), 1.27 (s, 9H), 1.41–1.46 (two doublets, $J=6$ Hz, 3H), 1.52–1.56 (m, 2H), 1.59–1.87 (m, 6H), 3.74 (s, 3H), 4.24–4.26 (t, $J=11.2$ Hz, 2H), 4.32–4.44 (m, 1H), 4.70–4.71, (m, 1H), 4.95–4.97 (m, 1H), 6.83–6.84 (d, $J=8.74$ Hz, 1H); ^{13}C NMR (125 MHz): −3.79, −4.72, 13.80, 17.94, 18.91, 22.40, 25.26, 28.95, 28.93, 29.25, 30.15, 31.57, 36.42, 41.09, 60.73, 62.14, 97.39, 115.19, 128.19, 173.19, 156.37; GC–MS: m/z 456 (M^+). Anal. calcd for $C_{25}H_{48}O_5Si$ (456.73) C, 65.74; H, 10.59. Found C, 65.52; H, 10.21%.