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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6571–6573

Enantioselective synthesis of tarchonanthuslactone via iterative hydrolytic kinetic resolution

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Received 17 June 2005; revised 4 July 2005; accepted 14 July 2005
Available online 1 August 2005

Abstract—A short and practical enantioselective synthesis of tarchonanthuslactone has been achieved in high diastereomeric excess using iterative Jacobsen's hydrolytic kinetic resolution and ring closing metathesis as the key steps.

Optically active *syn*- and *anti*-1,3-polyols/5,6-pyrones are ubiquitous structural motifs in various biologically active compounds[1] (Fig. 1). Fascinated by their broad range of biological activity and structural diversity in compounds ranging from simple carbohydrate to complex alkaloid and polyketides, synthetic chemists continue to pursue their synthesis[2] and the development of new methodologies. The lactone ring constitutes a structural feature of many natural products, particularly those that are Michael acceptors (α,β-unsaturated). They display pharmacological properties of interest such as plant growth inhibition as well as antifeedant, antifungal, antibacterial, and antitumor properties.[3,4] The simplest structure isolated which possesses a *syn*-1,3-diol/5,6-dihydropyran-2-one motif is the dihydrocaffeic ester, tarchonanthuslactone **1**.[5a,6] Tarchonanthuslactone was isolated by Bohlmann from *Tarchonanthustrilobus compositae*.[7] Caffeic acid has been established as an active principle, which lowers plasma glucose in diabetic rats.[8] Various methods for the synthesis of tarchonanthuslactone **1** have been described in the literature.[5] Nakata et al.[5g] determined the stereochemistry of **1** via a multistep synthesis, starting with optically active 1,3-butanediol. Most of the approaches to the 1,3-diol system are based on either enzymatic procedures[5a] or asymmetric methods such as Sharpless asymmetric dihydroxylation,[5b] chiral allylboration,[5c] use of a chiral sulfoxide to induce the chirality,[5d] and 1,3-asymmetric reduction.[5e,f]

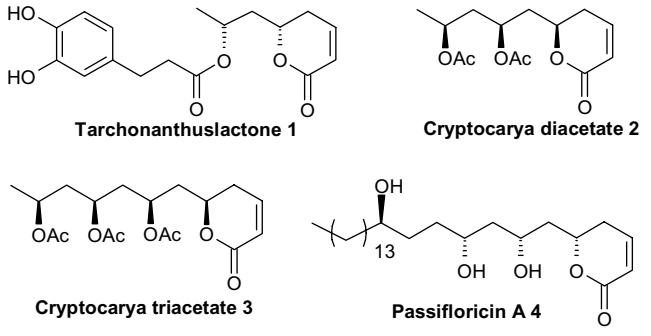

Figure 1.

In continuation of our interest aimed at developing syntheses of naturally occurring lactones,[9] we became interested in devising a simple and concise route to tarchonanthuslactone. In this paper, we report the stereoselective total synthesis of **1**, employing hydrolytic kinetic resolution (HKR)[10] and ring closing metathesis as the key steps. The HKR method involves the readily accessible cobalt based chiral salen complex **5** (Fig. 2) as catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol in high enantiomeric excess.

In designing a route to **1**, we chose propylene oxide as an appropriate starting material. Our synthesis of **1** requires two major reactions, Jacobsen's hydrolytic kinetic resolution to install the stereogenic centers and ring-closing metathesis to construct the δ-lactone moiety. As shown in Scheme 1, commercially available

Keywords: Tarchonanthuslactone; Jacobsen's hydrolytic kinetic resolution; Ring closing metathesis.
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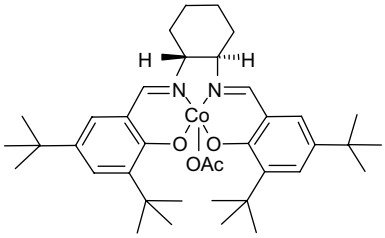
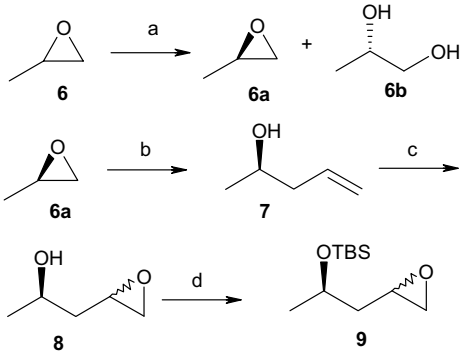
doi:10.1016/j.tetlet.2005.07.056



(*R*,*R*)-SalenCo(III)OAc complex **5**

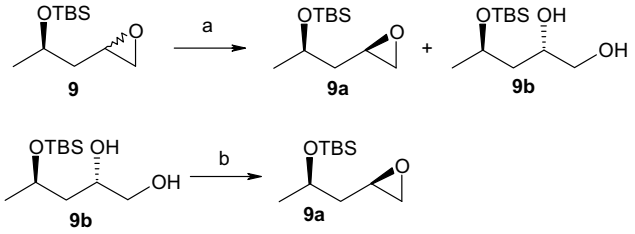
Figure 2.



Scheme 1. Reagents and conditions: (a) *R*,*R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 14 h, (46% for **6a**, 45% for **6b**); (b) vinylmagnesium bromide, THF, CuI, −20 °C, 12 h, 89%; (c) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 10 h, 96%; (d) TBDMS–Cl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 95%.

propylene oxide **6** was subjected to Jacobsen's HKR using (*R*,*R*)-salen-Co-OAc catalyst **5** (Fig. 2) to give (*R*)-propylene oxide **6a** as a single isomer; $[\alpha]_D^{25}$ +11.4 (neat); lit.[10d] $[\alpha]_D^{25}$ −11.6 (neat) (for (*S*)-propylene oxide), which was easily isolated from the more polar diol **6b** by distillation. (*R*)-Propylene oxide **6a** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **7** in excellent yield (Scheme 1). We then further proceeded to explore the stereoselective outcome of the epoxidation reaction with and without hydroxyl group protection. Toward this end the hydroxyl group of homoallylic alcohol **7** was first protected as the TBS ether, followed by epoxidation with *m*-CPBA. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti*:*syn*/3:1). The desired *syn* isomer **9a** was obtained only as a minor component. However, when epoxidation was carried out on alcohol **7** followed by hydroxy protection as the TBS–ether, the epoxide **9** was formed in favor of the desired *syn* isomer **9a** (*syn*:*anti*/1.2:1). The two diastereoisomers could not be differentiated on TLC.

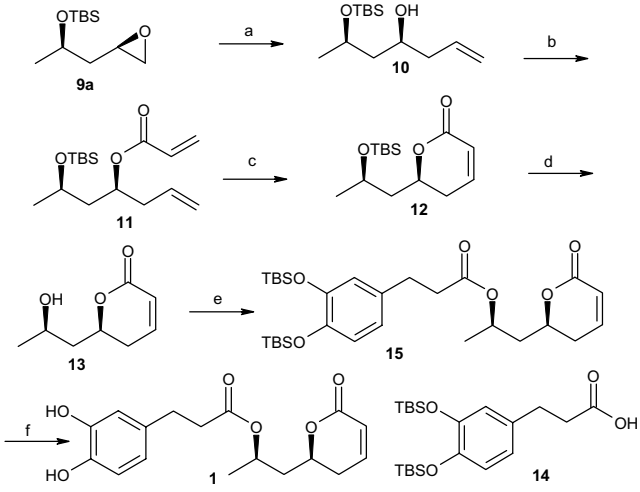
In order to improve the diastereoselectivity, we attempted the hydrolytic kinetic resolution method (HKR) as depicted in Scheme 2. Thus, the HKR was performed on **9** with (*R*,*R*)-salen-Co-OAc complex **5** (0.5 mol %) and water (0.55 equiv) in THF (0.55 equiv) to afford the epoxide **9a** as a single stereoisomer (as determined from the ^1H and ^{13}C NMR spectral analysis)[11] in 45% yield and the diol **9b** in 47% yield. Epoxide



Scheme 2. Reagents and conditions: (a) *R*,*R*-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 24 h, (45% for **9a**, 47% for **9b**); (b) (i) PivCl, Et_3N, cat. DMAP, rt; (ii) MsCl, Et_3N, DMAP, 0 °C to rt; (iii) K_2CO_3, MeOH, rt (61% for three steps).

9a could easily be separated from the more polar diol **9b** through silica gel column chromatography. As the HKR method provided the desired epoxide along with unwanted diol **9b** in almost equal amounts, we thought it would be appropriate to convert diol **9b** into the required epoxide **9a** via internal nucleophilic substitution of a secondary mesylate.[12] Accordingly chemoselective pivalation of diol **9b** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate with K_2CO_3 in methanol led to deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxide **9a** in 61% overall yield (Scheme 2).

With substantial amounts of **9a** in hand, we proceeded with the synthesis of **1** (Scheme 3). Thus opening of epoxide **9a** with vinylmagnesium bromide in the presence of CuI in THF at −20 °C furnished the homoallylic alcohol **10** in 86% yield. Alcohol **10** was then esterified with acryloyl chloride in the presence of Et_3N and a catalytic amount of DMAP to afford the acryloyl ester **11** in 89% yield. Subsequent ring closing metathesis of the ester with commercially available Grubbs' 1st



Scheme 3. Reagents and conditions: (a) vinylmagnesium bromide, THF, CuI, −20 °C, 1 h, 86%; (b) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 5 h, 89%; (c) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (10 mol %), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 8 h, 87%; (d) TBAF, THF, rt, overnight, 86%; (e) **14**, DCC, DMAP, CH_2Cl_2, 5 h, 85%; (f) TBAF, THF, 1 h, 84%.

generation catalyst[13] (10 mol %) in the presence of Ti(*i*-PrO)$_4$ (0.03 equiv) in refluxing CH_2Cl_2 for 8 h afforded the α,β-unsaturated δ-lactone **12**[14] in 87% yield. Desilylation of **12** with TBAF gave the hydroxy lactone **13** in 86% yield. Treatment of **13** with TBS protected dihydrocaffeic acid **14** using DCC and a catalytic amount of DMAP furnished compound **15** in 85% yield, which was deprotected with TBAF to give tarchonanthuslactone **1** in 84% yield. The physical and spectroscopic data of **1** were in full agreement with literature data.[5]

In conclusion, a practical and enantioselective synthesis of tarchonanthuslactone has been achieved using iterative hydrolytic kinetic resolution (HKR) to generate both the stereocenters and ruthenium catalyzed ring closing metathesis (RCM) to construct the δ-lactone moiety. The synthetic strategy described here has significant potential to synthesize a variety of other biologically important substituted 1,3-polyol-5,6-dihydropyran-2-one-containing natural products. Currently studies are in progress in this direction.

Acknowledgements

P.G. and S.V.N. thank UGC and CSIR, New Delhi, for financial assistance, respectively. We are grateful to Dr. M. K. Gurjar for his support and encouragement. Financial support from DST, New Delhi (Grant No. SR/S1/OC-40/2003) is gratefully acknowledged. This is NCL communication No. 6682.

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11. Spectral data of compound **9a**: $[\alpha]_D^{25}$ −11.4 (*c* 0.67, $CHCl_3$); IR (Chloroform): ν_{max} 3018, 2958, 2930, 1858, 1645, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.01–4.08 (m, 1H), 3.02–3.04 (m, 1H), 2.76–2.80 (m, 1H), 2.46–2.50 (m, 1H), 1.67–1.71 (m, 1H), 1.50–1.52 (m, 1H), 1.19 (d, $J = 6.3$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 66.3, 48.8, 45.8, 42.1, 25.4, 23.3, 17.6, −5.0, −5.3. Anal. Calcd for $C_{11}H_{24}O_2Si$ (216.39): C, 61.05; H, 11.18; Si, 12.98. Found: C, 61.12; H, 11.08; Si, 12.96.
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14. Spectral data of compound **12**: $[\alpha]_D^{25}$ −92.6 (*c* 0.84, $CHCl_3$); IR (Chloroform): ν_{max} 3019–2857, 1718, 1472, 1445, 1424, 1380, 1255, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.90 (ddd, $J = 10$, 4.2, 3.9 Hz, 1H), 6.04 (ddd, $J = 10$, 2.2, 2.2, 1H), 4.61 (dddd, $J = 8$, 8, 8, 5.1 Hz, 1H), 4.16–4.21 (m, 1H), 2.31–2.35 (m, 2H), 1.86 (ddd, $J = 14.3$, 8.1, 8.1 Hz, 1H), 1.62 (ddd, $J = 14.8$, 5.4, 4.2 Hz, 1H), 1.18 (d, $J = 6$ Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.2, 144.9, 121.1, 75.2, 64.6, 43.9, 29.4, 25.5, 23.1, 17.7, −4.5, −5.1. Anal. Calcd for $C_{14}H_{26}O_3Si$ (270.43): C, 62.18; H, 9.69; Si 10.39. Found: C, 62.09; H, 9.74; Si, 10.36.