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An efficient total synthesis of (−)-anamarine

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ABSTRACT

An efficient synthesis of (−)-anamarine is described using D(+)-mannitol and (*R*)-epichlorohydrin. The synthesis is achieved starting from easily accessible D(+)-mannitol using a selective benzoylation, regioselective epoxide ring opening, a selective acetonide deprotection, tosylation and cross metathesis reaction.

The δ-lactone ring system is found in a number of natural products and is also featured in many intermediates that are required for the synthesis of biologically important compounds.[1] In particular, α,β-unsaturated lactones have been shown to exhibit a wide range of biological activities.[2] Spicegerolide,[3] synrotolide,[4] hyptolide,[5] (−)-anamarine and (+)-anamarine[6] belong to this class of conjugated δ-lactones (Fig. 1), and it is believed that the presence of a Michael acceptor moiety in their skeleton is responsible for their biological activity. δ-Pyranone is a ubiquitous structural unit

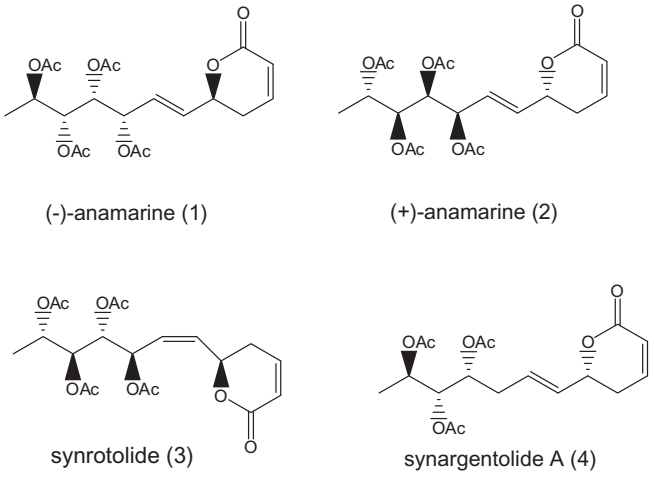
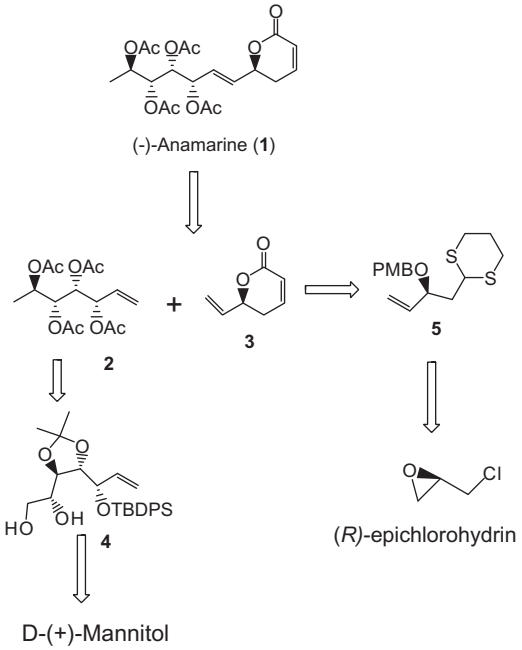


Figure 1. Chemical structure of polyhydroxy δ-pyranone products.



Scheme 1. Retrosynthesis of (−)-anamarine.

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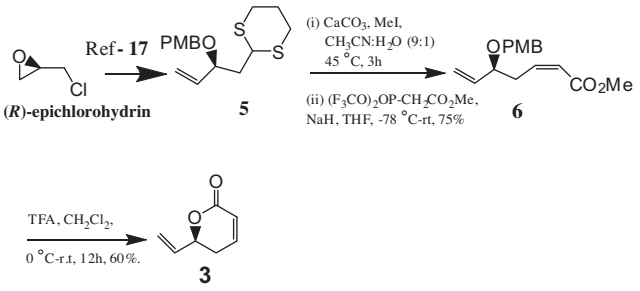


Scheme 2. Synthesis of fragment **3.**

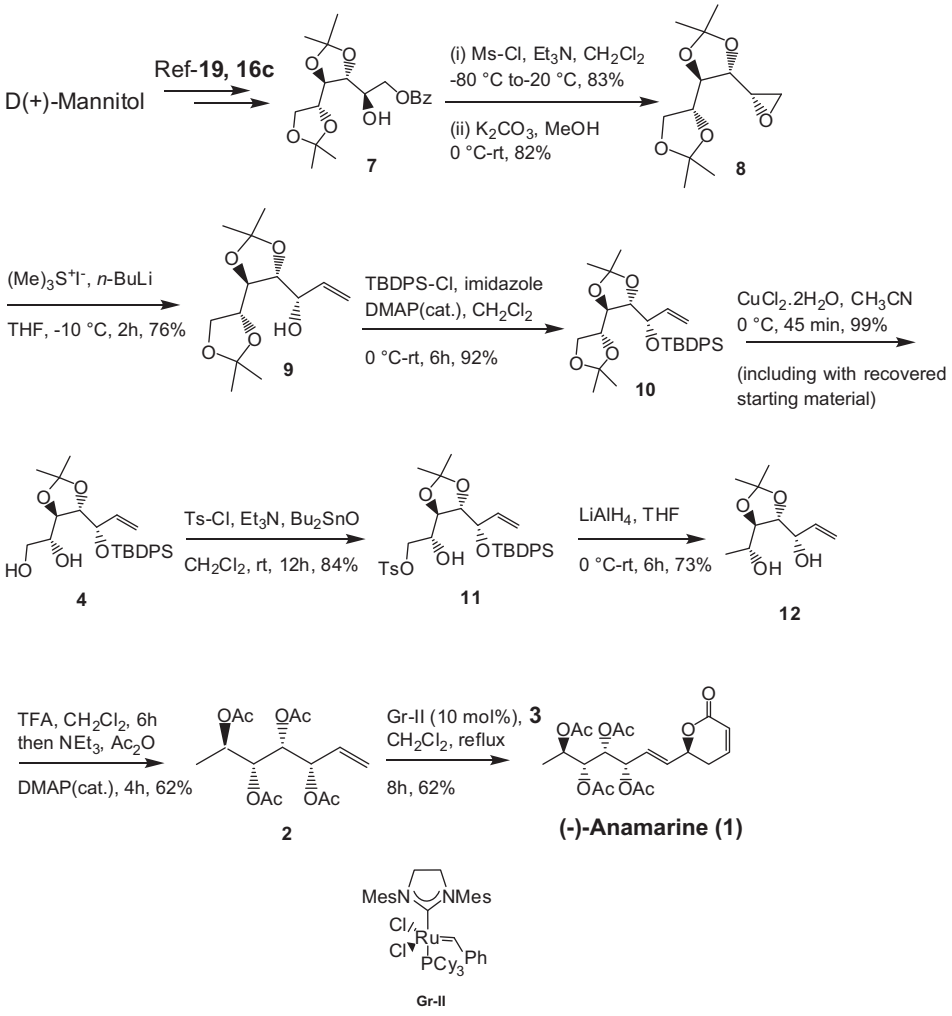
found in a number of bioactive natural products of therapeutic significance. Natural products and their analogues possessing this moiety exhibit a number of pharmacological properties such as anti-cancer[7] and anti-leukemic[8] activity, inhibits HIV protease,[9] induce apoptosis[10,11] and bioactivities in many other biological processes.[12]

Until now, three total syntheses were reported for (−)-anamarine (**1**) in the literature.[13–15] Early syntheses by Valverde et al.[13] and by Lorenz and Lichtenthaler[14] involved an arduous approach from glucanolactone precursors and suffered from low yields. Very recently, synthesis of (−)-anamarine was reported by Prasad et al.[15] from the D-(−)-tartaric acid based on a strategy of desymmetrization of tartaric acid amide. But all of them involved multiple steps and afforded rather low yields.

Recently, we have initiated a research programme for the total synthesis of bioactive natural products from chiral sources.[16,17] Our efforts on the use of D-(+)-mannitol as a six-carbon, four-hydroxy synthon culminated in the synthesis of a variety of natural products including bioactive lactones.[16c] Herein, we report the synthesis of (−)-anamarine from D-(+)-mannitol and (*R*)-epichlorohydrin. Our synthesis confirms the absolute configuration assigned to (−)-anamarine. As depicted in the retro synthetic analysis of (−)-anamarine, the crucial vinyl dihydropyran-2-one was prepared from (*R*)-epichlorohydrin. Compound **2** would be prepared from TBDPS, acetonide protected diol **4**. Precursor **4** would be constructed from natural chiral template D-Mannitol through the regioselective deprotection of acetonide and monobenzoylation (Scheme 1).

The vinyl lactone fragment **3** was prepared from (*R*)-epichlorohydrin. The PMB protected dithane **5** was prepared from (*R*)-epichlorohydrin.[17] The dithane **5** hydrolysis furnished the aldehyde,[18] which was subjected directly to a homologation using Still-Gennari conditions to give *Z*-unsaturated ester. The alkene ester **6** was submitted to cyclization in a one step reaction with TFA in CH_2Cl_2 conditions to obtain α,β-unsaturated lactone **3** with 60% yield (Scheme 2).

The other required component for accomplishing the final synthesis of (−)-anamarine (**1**) is the olefinic tetraacetate fragment **2** which was prepared from D-mannitol. The monobenzoyl alcohol



Scheme 3. Synthesis of (−)-anamarine.

7 is readily accessible from tri-*O*-isopropylidene-D-(+)-mannitol.[19,16c] The hydroxyl group of compound **7** was protected with Ms-Cl in the presence of Et_3N/CH_2Cl_2 followed by treatment with K_2CO_3/MeOH to give epoxide **8** in 82% yield. The epoxide **8** was regioselectively opened with $(Me)_3S^+I^-$, *n*-BuLi, THF, −10 °C and the resulting secondary allylic alcohol **9** was obtained in 76% yield.[20] The secondary allylic hydroxyl group in **9** was protected with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) and imidazole/DMAP to afford the silyl ether **10** in 92% yield. The 1,2-*O*-isopropylidene group of compound **10** was selectively deprotected by using $CuCl_2{\cdot}2H_2O$ in CH_3CN to afford diol **4** in 99% yield (with some starting material).[21] Diol **4** on monotosylation ($TsCl/Bu_2SnO/Et_3N/CH_2Cl_2$) provided **11** with 84% yields. The tosylated compound **11** followed by treatment with $LiAlH_4$ provided detosylated and desilylated olefin diol **12** in good yield.[22] Completion of the fragment synthesis required deprotection of acetonide **12** and acetylation of the four secondary alcohols. This was most conveniently achieved as a one-flask reaction in CH_2Cl_2 by addition of TFA/CH_2Cl_2/0 °C to rt stirred for 12 h and subsequently the addition of Et_3N/DMAP and acetic acid anhydride to afford tetracetate **2** in 62% yield. Finally coupling of both the fragments, that is, tetraacetate fragment **2** and the vinyl lactone fragment **3** was achieved via an olefin cross-metathesis reaction by using Grubb's second generation (**G-II**) catalyst[23] to give (−)-anamarine (**1**) in 62% yield (Scheme 3). Synthetic (−)-anamarine (**1**) exhibited identical spectral data[24] (IR, ^1H NMR, ^{13}C NMR and Mass) to that of the natural product.[13–15]

In summary, we have achieved the total syntheses of (−)-anamarine from a common precursor simply by changing the sequence of carbinol protection and thus allowing the formation of δ-lactone. Key features of the present route to (−)-anamarine are the efficient utilization of the C_2-symmetry of the starting material (D-(+)-mannitol), a selective benzoylation, a selective acetonide deprotection, detosylation, desilylation and a cross metathesis reaction. The syntheses of related compounds of this family are underway in our laboratory.

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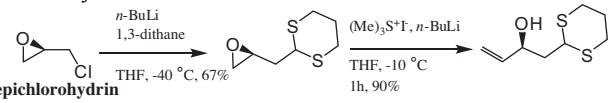
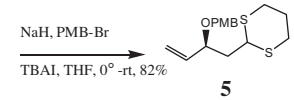
17. Ramesh, P.; Reddy, B. C.; Meshram, H. M. *Tetrahedron Lett.* **2012**. http://dx.doi.org/10.1016/j.tetlet.2012.04.118; The (*R*)-epichlorohydrin anion derived from 1,3-dithane to give epoxide in 67% yield. The epoxide was opened with $(Me)_3S^+I^-$, *n*-BuLi, THF, −10 °C and the resulting secondary allylic alcohol on treatment with p-methoxy benzyl bromide (PMB-Br) in the presence of NaH gave **5** in 82% yield



(***R***)-epichlorohydrin



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24. *Spectral data of selected compounds: (S)-6-vinyl-5,6-dihydro-2H-pyran-2-one (**3**):* Yellow liquid; $[\alpha]_D^{25}$ −94.3 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.47–2.42 (m, 2H), 4.98–4.88 (m, 1H), 5.31–5.27 (dd, 1H, *J* = 10.76 Hz), 5.43–5.37 (dd, 1H, *J* = 17.34 Hz), 6.06–5.88 (m, 2H), 6.89–6.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 29.3, 77.7, 117.8, 121.6, 134.8, 144.3, 163.7; EI-MS: *m/z* 125 (M^+H); ESI-HRMS: calcd 147.0429 (M^+Na); found 147.0421 (M^+Na). *(2R,3R,4R,5S)-hept-6-ene-2,3,4,5-tetrayl tetraacetate (**2**):* Light yellow oil; $[\alpha]_D^{30}$ +12.4 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.18 (d, 3H, *J* = 6.42 Hz), 2.0 (s, 3H), 2.09 (s, 6H), 2.41 (s, 3H), 2.80 (s, 1H), 4.92 (t, 1H, *J* = 6.42 Hz), 5.22 (dd, 1H, *J* = 6.61, 3.58 Hz), 5.26-5.36 (m, 4H), 5.68-5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 35.11, 40.02, 40.21, 40.29, 40.42, 86.85, 90.16, 91.09, 92.13, 139.70, 150.66, 189.15, 189.25, 189.30, 189.39; IR (KBr): 2932, 1741, 1223, 1032, 906 cm^{-1}; ESI-MS: *m/z* 353 [M^+Na]; ESI-HRMS: Calculated for $C_{15}H_{22}O_8Na$: 353.1212. Found: 353.1207. *(−)-Anamarine (**1**):* Gummy liquid; $[\alpha]_D^{25}$ −16.0 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.18 (d, 3H, *J* = 6.42 Hz), 2.03 (s, 3H), 2.07 (s, 6H), 2.13 (s, 3H), 2.50-

2.40 (m, 2H), 4.91 (quint, 1H, *J* = 6.5 Hz), 4.97 (td, 1H, *J* = 12.6, 7.7 Hz), 5.18 (dd, 1H, *J* = 6.9, 3.5 Hz), 5.31 (dd, 1H, *J* = 7.3, 3.5 Hz), 5.36 (dd, 1H, *J* = 7.0, 6.0 Hz), 5.90-5.75 (m, 2H), 6.07 (d, 1H, *J* = 9.5 Hz), 6.89 (ddd, 1H, *J* = 9.3, 5.0, 3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 15.8, 20.6, 20.86, 20.91, 21.0, 29.1, 67.3, 70.4, 71.6, 71.9, 75.8, 121.5, 125.5, 133.0, 144.5, 163.5, 169.76, 169.83, 169.86, 170.0; IR (KBr): 2935, 1745, 1223, 1028 cm–1; ESI-MS: *m/z* 444 [M^+NH_4], 449 [M^+Na]; ESI-HRMS for $C_{20}H_{26}O_{10}Na$ calcd 449.1424, found. 449.1422.