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Stereoselective total synthesis of polyrhacitide A

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ABSTRACT

Stereoselective total synthesis of polyketide lactone isolated from Chinese medicinal ant *Polyrhacis lamellidens* is described. Ring-closing metathesis followed by stereoselective intramolecular oxa-Michael addition reactions were used to construct the bicyclic lactone moiety in the molecule and L-malic acid was used as a chiral pool material

Ants from different parts of the world produce a wide range of interesting natural products having important biological functions and of considerable pharmacological interest.[1] Very recently Jiang and co-workers have isolated two new bicyclic lactones polyrhacitides A (**1**) and B (**2**)[2] (Fig. 1) from the Chinese medicinal ants *Polyrhacis lamellidens*, which have been used widely in China as traditional folk medicine for the treatment of rheumatoid arthritis and hepatitis.[3] The structure and absolute configuration of the molecules were determined by detailed spectroscopic studies. Although significant biological activities of polyrhacitides A (**1**) and B (**2**) remain unknown, extract of *p. lamellidens* showed significant analgesic and anti-inflammatory activities.[4] Therefore one might expect similar bioactivity of polyrhacitides A (**1**) and B (**2**). Due to their potential biological activities and unique structural features, as well as limited availability from the natural source (56.2 mg of A and 19.2 mg of B from 2 kg of ants) prompted us to develop an efficient strategy for their syntheses. While we were preparing this Letter, the first total synthesis of polyrhacitides A and B has appeared in the literature, where the catalytic asymmetric Overman esterification was utilized to install all the stereogenic centers.[5] In this Letter, we report the second stereoselective total synthesis of polyrhacitide A starting from L-malic acid.

Retrosynthetic analysis of polyrhacitide A revealed that the bicyclic lactone in the molecule could be constructed from compound **3** via an intramolecular oxa-Michael addition. The Michael acceptor that is, the α,β-unsaturated six-membered δ-lactone in **3** could be synthesized from the bis-olefinic compound **4**, which in turn could be obtained from the known compound **5** derived from L-malic acid (Scheme 1).

Our synthesis (Scheme 2) started from compound **5**, which was prepared from **6** according to the reported procedure.[6a,b] Protection of the secondary hydroxyl group of **5** as its benzyl ether followed by acetonide deprotection under acidic conditions furnished diol **8**[6c] in 90% yield over two steps. Chemoselective tosylation of the primary alcohol followed by tosyl displacement with the vicinal hydroxyl group under basic conditions furnished epoxide **9**[6c] in 70%. Crucial opening of the epoxide **9** at the less substituted carbon atom with the anion generated from dithiane **9a** using *n*-butyllithium in THF under argon atmosphere gave compound **10** in 80% yield.[7] Deprotection of the dithioacetal group with $AgNO_3$ in aqueous ethanol at 60 °C furnished keto compound **11** in 78% yield.[8]

Hydroxyl directed stereoselective reduction of the keto group using $NaBH_4$ and Et_2BOMe[9] in THF/MeOH (4:1) at −78 °C gave 1,3-*syn* diol **12** in 83% (dr 95:5). Acetonide protection of the 1,3-diol using 2,2-dimethoxy propane in the presence of catalytic amount CSA yielded compound **13** in 95% yield. We planned to introduce the C4-OH center via asymmetric allylation, but when the aldehyde obtained from the olefinic compound **13** was subjected to asymmetric allylation,[10] using Brown's[10a] as well as Keck[10b] protocols gave poor yields (~5%). This unexpected result forced us to do the substrate-controlled allylation.[11] Thus the aldehyde on treatment with allylmagnesium bromide in ether gave compound **14** (2.5:1) as inseparable diastereomeric mixtures. On acylation with acryloyl chloride compound **14** gave the separable diastereomers **4** (major) and **4a** (minor). To establish the stereochemistry at C4 compound **4a** was converted to compound **15a** in three steps. In the ^{13}C NMR spectrum of compound **15a**, the methyls of the C4:C6-*O*-isopropylidene group resonating at δ 24.6 and 24.8 and the ketal carbon at δ 100.1 confirmed their anti relationship according to the reports of Rychnovsky[12a] and

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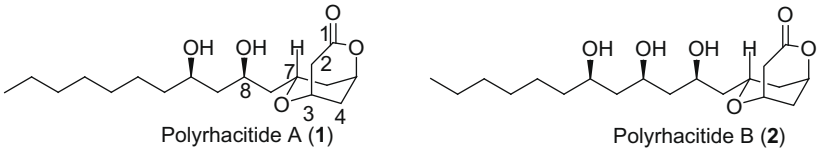
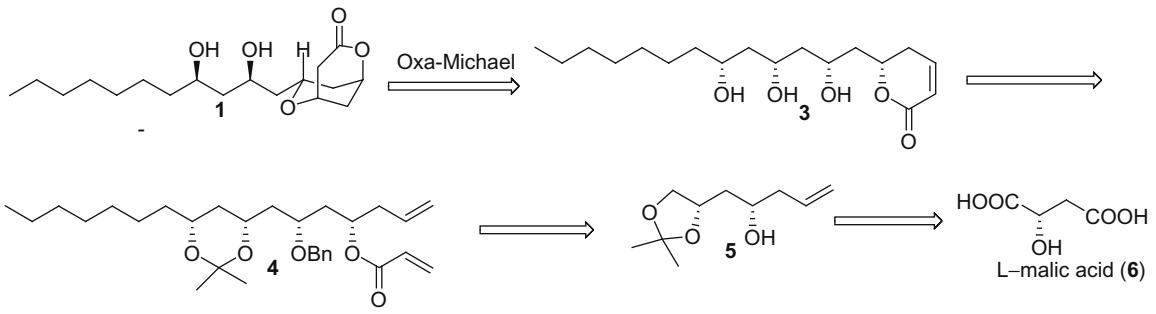
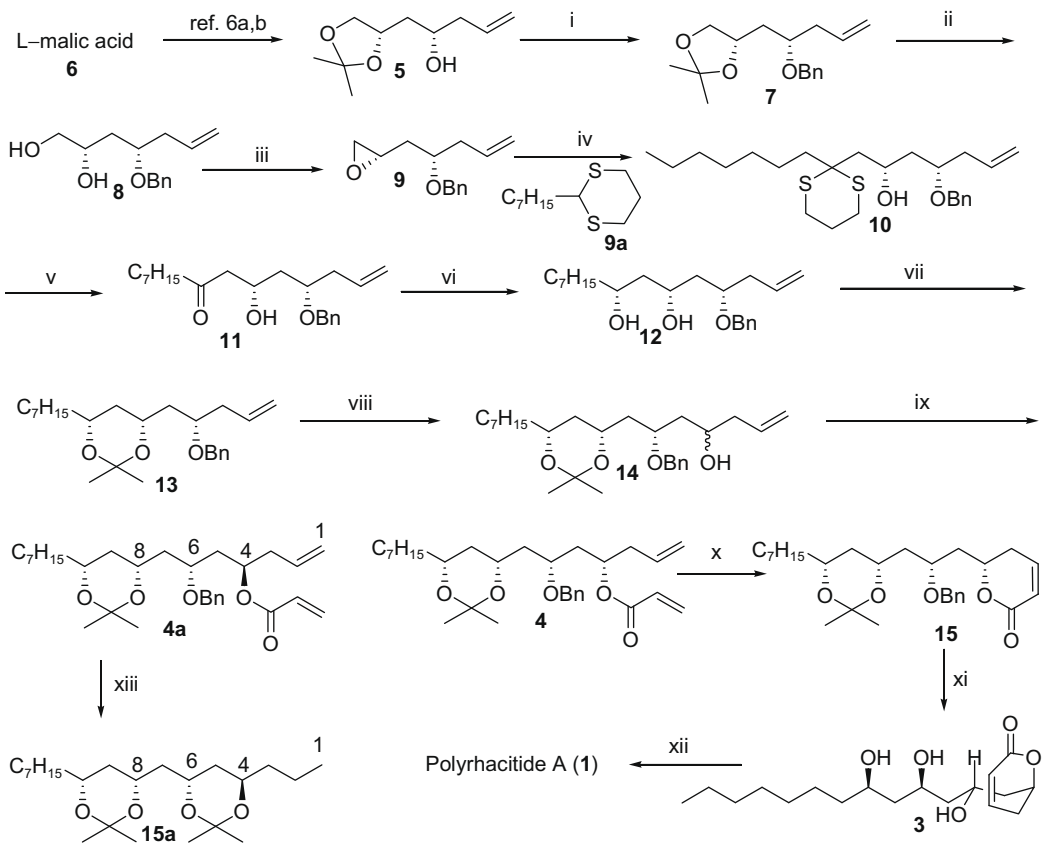


Figure 1. Structure of polyrhacitides A and B.

Evans.[12b] Therefore in the major isomer **4**, the C4-OH and C6-OH had 1,3-*syn* relationship. Next, the bis-olefinic compound **4** was subjected to RCM reaction using Grubbs 2nd generation catalyst[13] in CH_2Cl_2 to give compound **15**[15a] in 80% yield. Global deprotection of the compound **15** with $TiCl_4$ in CH_2Cl_2 at 0 °C gave compound **3**, which on treatment with DBU[14] in THF at 0 °C afforded polyrhaci-



Scheme 1. Retrosynthetic analysis of polyrhacitide A.



Scheme 2. Reagents and conditions. (i) NaH, BnBr, TBAI (cat), DMF, 0 °C to rt, 24 h, 95%; (ii) AcOH, EtOH/H_2O, (2.5:1.), 0 °C to rt, 24 h, 95%; (iii) (a) TsCl, Et_3N, CH_2Cl_2, DMAP, 0 °C to rt, 1 h; (b) K_2CO_3, MeOH, 0 °C to rt, 1 h, 70% over two steps; (iv) **9a**, *n*BuLi, THF, rt, 80%; (v) $AgNO_3$, EtOH/H_2O (10:1), 60 °C, 45 min, 78%; (vi) Et_2BOMe, $NaBH_4$, THF/MeOH (4:1), −78 °C, 3 h, 83%, dr 95:5; (vii) 2,2-DMP, CSA (cat), CH_2Cl_2, 0 °C to rt, 4 h, 95%; (viii) OsO_4, NMO, acetone/H_2O (1:1), 12 h; (b) $NaIO_4$, THF/H_2O (1:1), 0 °C to rt, 1 h; (c) allylmagnesium bromide, Et_2O, 0 °C, 1 h; 60% over three steps, dr = 2.5:1; (ix) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min, 68% **4** and 27% **4a**; (x) Grubbs 2nd generation catalyst, CH_2Cl_2, 50 °C, 12 h, 80%; (xi) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 30 min, 75%; (xii) DBU, THF, 0 °C to rt, 36 h, 90%; (xiii) (a) K_2CO_3, MeOH, rt, 1 h; (b) H_2, Pd/C, MeOH; (c) 2,2-DMP, CSA (cat), CH_2Cl_2, 0 °C to rt, 4 h, 75%.

tide A (**1**) in 72% over two steps, whose analytical data, (^{1}H and ^{13}C)[15b] and the specific rotation (synthetic $[\alpha]_D^{25}$ = +5.5, *c* 0.09, MeOH, reported $[\alpha]_D^{25}$ = +8.3, *c* 0.6, MeOH) were in good agreement with the literature values.

In conclusion, we have achieved the stereoselective total synthesis of polyrhacitide A (**1**) from L-malic acid. Currently we are working on the total synthesis of polyrhacitide B, with a little modification of the above strategy, which will be reported in due course.

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15. (a) *Analytical data of compound* **15**: R_f = 0.5 (silica gel, 20% EtOAc in hexane); $[\alpha]_D^{28}$ −46.31 (*c* 0.19, $CHCl_3$); IR (neat): ν_{max} 2924, 2855, 1728, 1460, 1383, 1249, 1109, 741, 701 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 6.79 (ddd, *J* = 9.0, 6.5, 2.4 Hz, 1H), 6.0 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.58 (m, 1H), 4.53 & 4.45 (two d, *J* = 11.8 Hz, 2H), 3.98 (m, 1H), 3.77 (pent, *J* = 5.9 Hz, 1H), 3.73 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.14 (m, 1H), 1.88 (m, 1H), 1.63 (m, 1H), 1.4 (s, 3H), 1.36 (s, 3H), 1.26–1.24 (m, 15H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.5, 145.1, 138.3, 128.4, 128.1, 127.7, 121.3, 98.3, 75.3, 71.3, 70.3, 69.0, 65.6, 39.5, 38.8, 37.1, 36.4, 33.7, 32.0, 30.1, 29.7, 29.3, 29.2, 29.0, 24.9, 22.6, 14.1; MS (ESI): *m*/*z* (%) 459 (50) $[M+H]^+$, 481 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{28}H_{42}O_5$ Na $[M+Na]^+$ 481.2909, found 481.2929.
(b) *Analytical data for polyrhacitide A*: Mp: 65 °C. R_f = 0.5 (silica gel, 80% EtOAc in hexane); $[\alpha]_D^{28}$ +5.5 (*c* 0.09, MeOH); IR (neat): ν_{max} 3421, 3315, 2923, 2854, 1729, 1454, 1340, 1201, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.88 (m, 1H), 4.40 (br s, 1H), 4.11–4.01 (m, 2H), 3.83 (m, 1H), 2.90 (dt, *J* = 19.3, 1.6 Hz, 1H), 2.81 (dd, *J* = 19.3, 5.2 Hz, 1H), 2.05 (m, 1H), 2.02 (m, 1H), 1.94 (ddd, *J* = 14.0, 4.0, 2.0 Hz, 1H), 1.71 (dt, *J* = 14.7, 9.5 Hz, 1H), 1.67–1.61 (m, 2H), 1.59 (dt, *J* = 14.4, 2.7 Hz, 1H), 1.54–1.44 (m, 3H), 1.41–1.36 (m, 2H), 1.32–1.20 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 72.7, 72.5, 72.1, 67.0, 66.0, 43.2, 42.8, 37.7, 37.2, 36.4, 31.8, 29.6, 29.4, 29.3, 25.4, 22.6, 14.1; MS (ESI): *m*/*z* (%) 329 (30) $[M+H]^+$, 351 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{18}H_{32}O_5$ Na $[M+Na]^+$ 351.2154, found 351.2147.