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Stereoselective total synthesis of (+)-polyrhacitide A

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ABSTRACT

A facile stereoselective total synthesis of secondary metabolite (+)-polyrhacitide A is described. Stereoselective aldol reaction, Horner–Wardsworth–Emmons reaction, Evans acetal intramolecular oxa-Michael reaction and diastereoselective *syn* reduction reaction are the key steps involved in the target synthesis.

Secondary metabolites continue to address several problems towards human health care despite the fact that they are not involved in direct growth or reproduction of the producing organism. The secondary metabolites comprising macrolide peptides, alkaloids, terpenoids and polyketides obtained from several sources have been found to display potent antibiotic, antifungal and antiviral properties.[1] Very recently, Jiang and Kouno have reported the isolation of two unusual bicyclic lactone unit containing compounds polyrhacitides A **1** and B **2** from the Chinese ant species *Polyrhacis lamellidens* Smith.[2] This unit was also found to be present as a constituent in the molecules obtained from the tree extracts of Cryptocarya species **3–5** (Fig. 1).[3] The ant *P. lamellidens* has been used as a folk medicine in the treatment of rheumatoid arthritis and hepatitis in China and the crude MeOH extract of this ant was also found to display significant analgesic and anti-inflammatory effects.[4] The structures of polyrhacitides A and B were identified based on exhaustive NMR studies and the absolute configuration was assigned based on acetonide and Mosher's ester method. As these natural products are available in very scarce amounts, total synthesis becomes a viable approach for their availability towards exploring the biological properties. While there is only one total synthesis for polyrhacitides A and B reported by Menz and Kirsch[5] involving an iterative approach, the strategy requires lengthy steps and thus the new synthetic strategies are well desired.

In continuation of our long-term projects involving the total synthesis of polyketides,[6] we herein wish to report the stereoselective total synthesis of polyrhacitide A by successful implementation of the strategies developed towards the synthesis of the all syn 1,3-polyol functionalities.

Retrosynthetically, it was envisaged that the target compound could be obtained from the key precursor **6** which can undergo acid-mediated one-pot dibenzylidene acetal deprotection, lactonization and oxa-Michael reaction. The precursor **6** can be synthesized from amide **8** following a seven-step sequence through an intermediate **7** involving stereoselective reduction, Horner–Wadsworth–Emmons–Wittig reaction and Evans acetal intramolecular conjugate addition reaction as the key steps. The amide **8** in turn can be obtained from **9** involving the auxillary cleavage, followed by a Wittig reaction and subsequent Evans acetal intramolecular

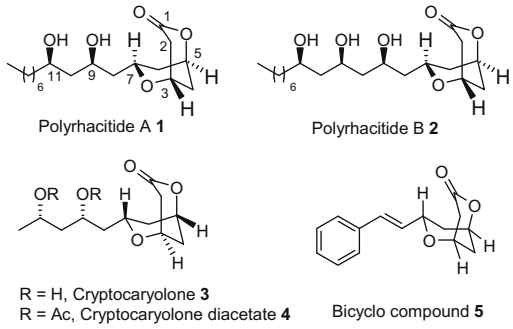
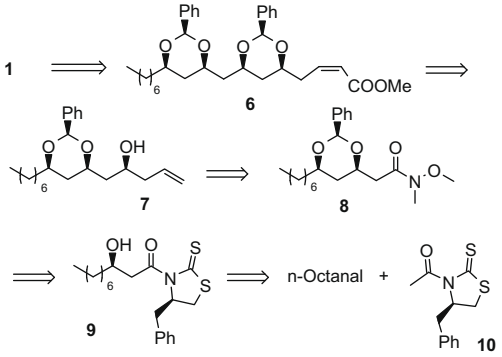


Figure 1.



Scheme 1. Retrosynthesis.

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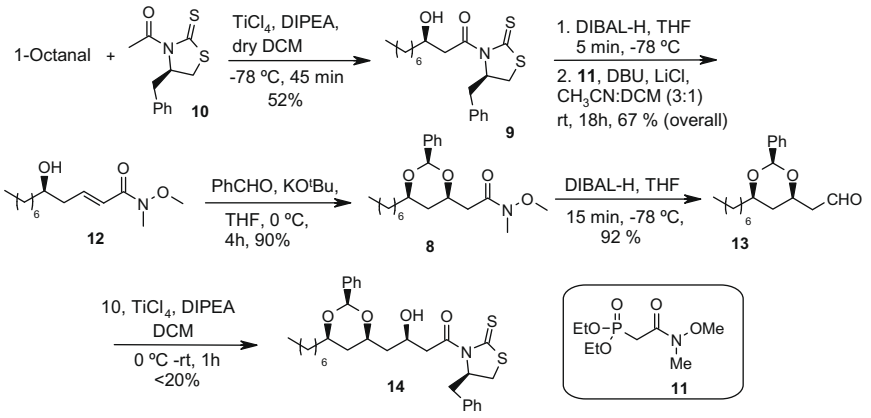
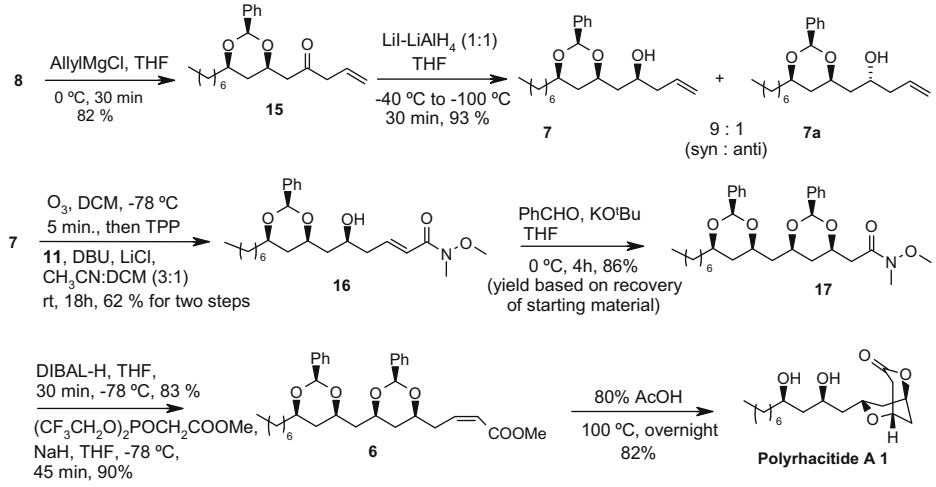


Scheme 2.



Scheme 3.

oxa-Michael reaction. Compound **9** in turn is obtained from modified Evans aldol reaction of *n*-octanal and *N*-acetyl thiazolidinethione **10** (Scheme 1).

An important element to our synthetic strategy is the utility of asymmetric aldol reaction to establish the initial asymmetry. Thus, our synthesis commenced with an aldol reaction[7] of (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone and *n*-octanal in the presence of titanium(IV) chloride and diisopropylethylamine to install the first stereogenic centre yielding **9** as the major diastereomer (Scheme 2). The compound **9** was treated with DIBAL-H and subjected to a Wittig–Horner reaction[8] with *N*-methoxy *N*-methyl diethylphosphonoacetamide **11**[9] to obtain the α,β-unsaturated amide **12** exclusively as *E*-isomer. The compound **12** was subjected to an Evans acetal intramolecular oxa-Michael reaction with benzaldehyde and potassium *tert*-butoxide to yield the product **8** in 90% yield [10] installing the desired 2nd stereocentre.

The amide **8** was reduced with DIBAL-H to the corresponding aldehyde **13**. With the aldehyde in hand, we attempted similar iterative steps to generate further two stereocentres. However, as the aldol reaction was very sluggish and the yield was very low (<20%) for the product **14**, we had to alter our approach for installing the third stereocentre with better yields.

Thus, the compound **8** was treated with allyl magnesium chloride to get ketone **15**. The β-alkoxy ketone **15** was subjected to chelation-controlled *syn* reduction[11] using $LiAlH_4$ and LiI to get the desired homoallyl alcohol **7** along with an easily separable isomer **7a** in 9:1 ratio. Compound **7** was subjected to ozonolysis to get the corresponding aldehyde and was immediately treated with **11** in the presence of DBU and LiCl to get the α,β-unsaturated amide **16**. The compound **16** was again subjected to Evans acetal-forming reaction to install the fourth stereocentre yielding the product **17**. With the installation of four stereocentres, the rest was to set a stage for building up the six-membered lactone ring formation. Towards this, the compound **17** was treated with DIBAL-H to get the corresponding aldehyde and then subjected to Horner–Wittig reaction with bis(2,2,2-trifluoromethyl)(methoxy carbonylmethyl)phosphonate[12] to get the key precursor **6** with all *syn* bis benzylidene-protected tetrol and an unsaturated ester. Exposure of this key precursor **6** to 80% AcOH[13] at 100 °C for 18 h yielded the desired bicyclic product polyrhacitide A (Scheme 3). The analytical data[14] were found to be identical and optical rotation was comparable with the reported data of both the natural[2] and synthetic products.[5]

In conclusion, a concise total synthesis of polyrhacitide A has been accomplished in 12 steps. Modified Evans aldol approach, Evans acetal intramolecular oxa-Michael reaction and chelation-controlled stereoselective keto reduction reactions are the key steps involved in the target synthesis. This approach may find wide utility in exploring the synthesis of other diastereomers for their biological evaluation. The total synthesis of polyrhacitide B is being currently investigated following the above-mentioned synthetic strategy.

Acknowledgement

G.R. and B.G. thank CSIR, New Delhi for financial assistance.

References and notes

1. For recent literature see: (a) Arif, T.; Bhosale, J. D.; Kumar, N.; Mandal, T. K.; Bendre, R. S.; Lavekar, G. S.; Dabur, R. *J. Asian Nat. Prod. Res.* **2009**, *11*, 621–638; (b) Piel, J. *Nat. Prod. Rep.* **2009**, *26*, 338–362; (c) Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290–2303; (d) Lu, X.-L.; Xu, Q.-Z.; Liu, X.-Y.; Cao, X.; Ni, K.-Y.; Jiao, B.-H. *Chem. Biodivers.* **2008**, *5*, 1669–1674; (e) Itokawa, H.; Morris-Natschke, S. L.; Akiyama, T.; Lee, K.-H. *J. Nat. Med.* **2008**, *62*, 263–280; (f) Wen, Z.; Guo, Y.-W.; Yucheng, G. *Curr. Med. Chem.* **2006**, *43*, 303–332; (g) Croteau, R.; Kutchan, T. M.; Lewis, N. G. *Natural Products (Secondary Metabolites)*; *Biochemistry & Molecular Biology of Plants*, Rockville, Maryland, 2000, pp 1250–1318.; (h) Pietra, F. *Nat. Prod. Rep.* **1997**, 453–464.
2. Jiang, Z. H.; Yang, Q. X.; Tanaka, T.; Kouno, I. *J. Nat. Prod.* **2008**, *71*, 724–727.
3. (a) Drewes, S. E.; Sehlapelo, B. M.; Horn, M. M.; Scott-Shawt, R.; Sandor, P. *Phytochemistry* **1995**, *38*, 1427–1430; (b) Drewes, S. E.; Horn, M. M.; Rameswar, N. S.; Ferreira, D. *Phytochemistry* **1998**, *49*, 1683–1687.
4. Kou, J.; Ni, Y.; Li, N.; Wang, J.; Liu, L.; Jiang, Z.-H. *Biol. Pharm. Bull.* **2005**, *28*, 176–180.
5. Menz, H.; Kirsch, S. F. *Org. Lett.* **2009**, *11*. 5634-563.
6. (a) Srihari, P.; Rajendar, G.; Rao, R. S.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 5590–5592; (b) Sabitha, G.; Gopal, P.; Yadav, J. S. *Helv. Chim. Acta* **2008**, *91*, 2240–2246; (c) Sabitha, G.; Bhaskar, V.; Reddy, S. S.; Yadav, J. S. *Tetrahedron* **2008**, *64*, 10207–10213; (d) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469–1471.
7. For the synthesis of *N*-acetylthiazolidinethione complex see: (a) Yadav, J. S.; Naveen Kumar, V.; Srinivasa Rao, R.; Srihari, P. *Synthesis* **2008**, 1938–1942; (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777; For the acetate syn aldol approach see: (c) Hodge, M. B.; Olivo, H. F. *Tetrahedron* **2004**, *60*, 9397–9403; (d) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. J. *Org. Chem.* **2001**, *66*, 894–902.
8. Etayo, P.; Badorrey, R.; Diaz-de-Villegas, M. D.; Galvez, J. A. *J. Org. Chem.* **2007**, *72*, 1005–1008.
9. Compound **11** was synthesized in three steps from bromoacetyl bromide according to: Nuzillard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *29*, 3779–3780.
10. Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446–2453. Yield has been calculated based on recovery of the starting material..
11. (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419–5422; (b) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783–8788.
12. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.
13. Similar procedure was adopted following: Hayakawa, H.; Miyashita, M. *Tetrahedron Lett.* **2007**, *47*, 707–711. Longer reaction time was required to get the desired bicyclic lactone exclusively.
14. Spectral data for few selected compounds: (*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxydecan-1-one (**9**): Yellow oil, $[\alpha]_D^{30}$ −169 (*c* 1.2 , $CHCl_3$); IR (neat): 3155, 2925, 2854, 1695, 1603, 1490, 1262, 1162, 1039, 1007, 745, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.28 (br s, 9H), 1.40–1.61 (m, 3H), 2.68–2.82 (br s, 1H), 2.90 (d, *J* = 11.5 Hz, 1H), 3.0–3.18 (m, 2H), 3.19–3.26 (dd, *J* = 3.9, 13.2 Hz, 1H); 3.40 (ddd, *J* = 0.7, 7.1, 11.5, Hz, 1H), 3.64 (dd, *J* = 2.4, 17.7 Hz, 1H), 4.10–4.19 (m, 1H), 5.36–5.44 (m, 1H), 7.24–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 22.6, 25.5, 29.2, 29.4, 31.8, 32.0, 36.3, 36.8, 45.8, 67.8, 68.2, 127.2, 128.8, 129.3, 136.3, 173.2, 201.3. MS-ESIMS: *m*/*z* 380 $(M+H)^+$. HRMS calcd for $C_{20}H_{29}NO_2NaS_2$: 402.1537, found 402.1538. 2-((2*R*,4*R*,6*R*)-6-heptyl-2-phenyl-1,3-dioxan-4-yl)-*N*-methoxy-*N*-methylacetamide (**8**): pale yellow oil: $[\alpha]_D^{30}$ +22 (*c* 1.0, $CHCl_3$), IR (neat): 2927, 2854, 2073, 1646, 1455, 1113, 1019, 771, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7, Hz, 3H), 1.22–1.55 (m, 12H), 1.60–1.70 (m, 1H), 1.77 (dt, *J* = 2.0, 12.8 Hz, 1H), 2.48 (dd, *J* = 6.2, 15.6 Hz, 1H), 2.92 (dd, *J* = 6.7, 14.9 Hz, 1H), 3.16 (s, 3H), 3.65 (s, 3H), 3.77–3.87 (m, 1H), 4.27–4.38 (m, 1H), 5.51, (s, 1H), 4.25–7.34 (m, 3H), 7.41–7.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): 14.2, 22.7, 25.1, 29.3, 29.6, 31.9, 36.0, 37.0, 38.2, 61.2, 65.0, 73.4, 76.6, 100.6, 126.1, 127.9, 128.3, 138.8, 171.2; MS-ESIMS: *m*/*z* 364 $(M+H)^+$, 386 $(M+Na)^+$; HRMS calcd for $C_{21}H_{33}NO_4Na$: 386.2307, found 386.2324. (*S*)-1-((2*R*,4*S*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl)pent-4-en-2-ol (**7**): colourless liquid, $[\alpha]_D^{30}$ −3.9 (*c* 1.1, $CHCl_3$); IR (neat): 3460, 2925, 1854, 2361, 1641, 1459, 1114, 1019, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.21–1.39 (br s, 9H), 1.41–1.57 (m, 3H), 1.58–1.83 (m, 4H), 2.25 (t, *J* = 6.6 Hz, 2H), 3.18 (s, 1H), 3.77–3.87 (m, 1H), 3.92–4.01 (m, 1H), 4.0–4.15 (m, 1H), 5.08 (s, 1H), 5.13 (d, *J* = 7.1 Hz, 1H), 5.55 (s, 1H), 5.77–5.92 (m, 1H), 7.29–7.38 (m, 3H), 7.43–7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 22.6, 24.9, 29.1, 29.4, 31.7, 35.7, 37.0, 41.9, 41.9, 70.3, 76.9, 77.3, 100.5, 117.5, 125.9, 128.1, 128.6, 134.7, 138.3. MS-ESIMS: *m*/*z* 369 $(M+Na)^+$; HRMS calcd for $C_{22}H_{34}NaO_3$: 369.2303, found 369.2318. (*Z*)-Methyl-4-((2*S*,4*S*,6*S*)-6-(((2*R*,4*R*,6*R*)-6-heptyl-2-phenyl-1,3-dioxan-4-yl)-methyl)-2-phenyl-1,3-dioxan-4-yl)but-2-enoate (**6**): pale yellow viscous liquid, $[\alpha]_D^{30}$ −11 (*c* 1.4, $CHCl_3$); IR (neat): 2923, 2854, 2362, 1723, 1647, 1458, 1179, 1018, 759, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.24–1.34 (m, 10H), 1.42–1.81(m, 7H), 2.09–2.22 (m, 1H), 2.86–2.97 (m, 1H), 3.04–3.16 (m, 1H), 3.71 (s, 3H), 3.76–3.86 (m, 1H), 3.94–4.16 (m, 3H), 5.52 (s, 1H), 5.54 (s, 1H), 5.90 (d, *J* = 11.5 Hz, 1H), 6.42–6.53 (m, 1H), 7.31–7.40 (m, 6H), 7.47–7.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 22.6, 25.0, 29.2, 29.5, 31.8, 35.1, 35.9, 36.3, 36.8, 41.7, 51.0, 73.0, 73.1, 75.9, 76.9, 100.5, 100.6, 120.8, 126.0, 126.0, 128.1, 128.1, 128.5, 128.6, 138.6, 138.9, 145.7, 166.7. MS-ESIMS: *m*/*z* 537 $(M+H)^+$, 559 $(M+Na)^+$; HRMS calcd for $C_{33}H_{44}O_6Na$: 559.3035, found 559.3063. Polyrhacitide-A **1**: colourless solid, mp = 68–70 °C. $[\alpha]_D^{30}$ +7.8 (*c* 0.4, MeOH), IR (neat): 3459 (O–H), 2925, 2854, 1729 (C=O), 1384, 1220, 1076, 772, 677 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.24–1.42 (m, 9H), 1.44–1.76 (m, 8H), 1.99–2.07 (m, 3H), 2.77 (dd, *J* = 5.1, 19.2 Hz, 1H), 2.88 (d, *J* = 19.2 Hz, 1H), 3.76–3.82 (m, 1H, H-11), 4.0–4.07 (m, 2H, H-7, 9), 4.38 (br s, 1H, H-3), 4.83–4.86 (m, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): 14.3, 22.8, 25.5, 29.4, 29.7, 29.7, 31.9, 36.5, 37.4, 37.9, 43.1, 43.5, 66.1 (C-3), 67.0 (C-7), 72.0 (C-11), 72.1 (C-9), 72.6 (C-5), 168.2 (C-1). MS-ESIMS: *m*/*z* 329 $(M+H)^+$, 351$(M+Na)^+$; HRMS calcd for $C_{18}H_{32}O_5Na$: 351.2147, found 351.2160.