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First total synthesis of verbalactone, a macrocyclic dilactone isolated from *Verbascum undulatum*

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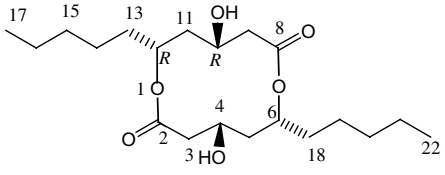
Abstract—Verbalactone, a new macrocyclic dilactone was synthesized efficiently in a steroselective manner involving a Barbier–Grignard reaction, a Sharpless asymmetric dihydroxylation, monotosylation, epoxidation, ring opening of the epoxide, hydrolysis and lactonization. A δ-lactone, (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide was also formed along with the dimeric lactone.

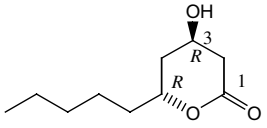
Verbalactone[1] **1** is a macrocyclic dilactone isolated from the roots of *Verbascum undulatum* Lam., a biennial plant of the genus *Verbascum* that belongs to the family Scrophulariaceae. This molecule showed activity against three Gram-positive bacteria with optimum activity MIC = 62.5 μg/mL and five Gram-negative bacteria with optimum activity MIC = 125 μg/mL[1,2] and was found to exhibit interesting antibacterial properties. This macrocyclic lactone is a symmetrical dimer of the lactone **2** (a δ-lactone), (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide[3] and which is a potent inhibitor of the enzyme HMG-CoA reductase. The NMR profile of **1** is very similar to the monomeric lactone of (3*R*,5*R*)-dihydroxydecanoic acid. The structure and the absolute stereochemistry of this lactone, 4*R*,6*R*,10*R*,12*R*,4,10-dihydroxy-2,8-dioxo-6,12-dipentyl-1,7-dioxacyclododecane, were determined by spectroscopic methods and chemical correlation. It is the first example of a 1,7-dioxacyclododecane unit being present in the ring system of a natural product (Scheme 1).

Due to its interesting antibacterial activity and our interest in the chemistry of macrolide antibiotics,[4] we were attracted towards its total synthesis. Herein we wish to report the first asymmetric total synthesis of this lactone.

The retrosynthesis envisaged for the synthesis of verbalactone is shown in Scheme 2. The dimeric lactone can be disconnected as shown in the Scheme. The resulting 3,5-dihydroxy acid **3** could be synthesized from the cyanide **4**, which in turn can be obtained from a precursor such as **5** through a regioselective ring opening strategy with CN^- as the nucleophile.[5] The epoxide **5**



Verbalactone **1**



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Scheme 1.

Keywords: Macrocyclic dilactone; Verbalactone; Barbier–Grignard reaction; Sharpless asymmetric dihydroxylation; Tosylation; HMG-CoA reductase; Kinetic resolution; Lactonization.
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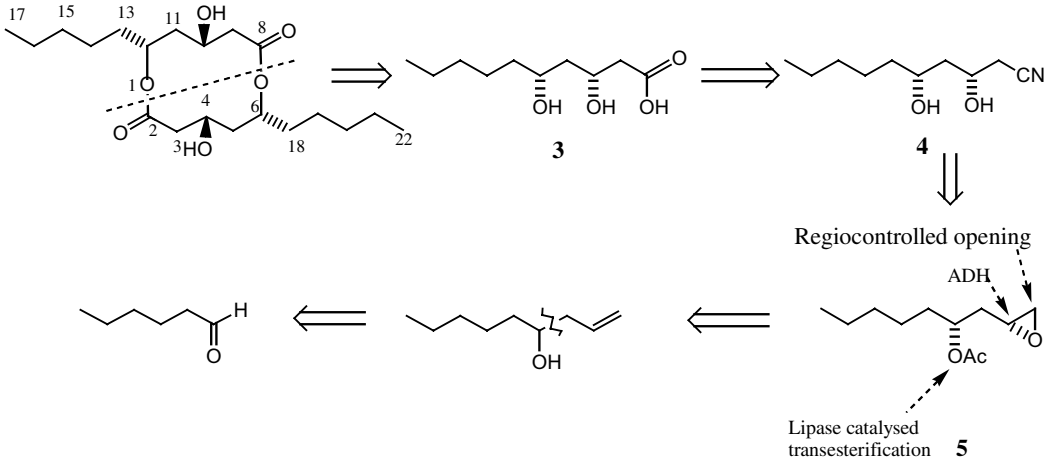
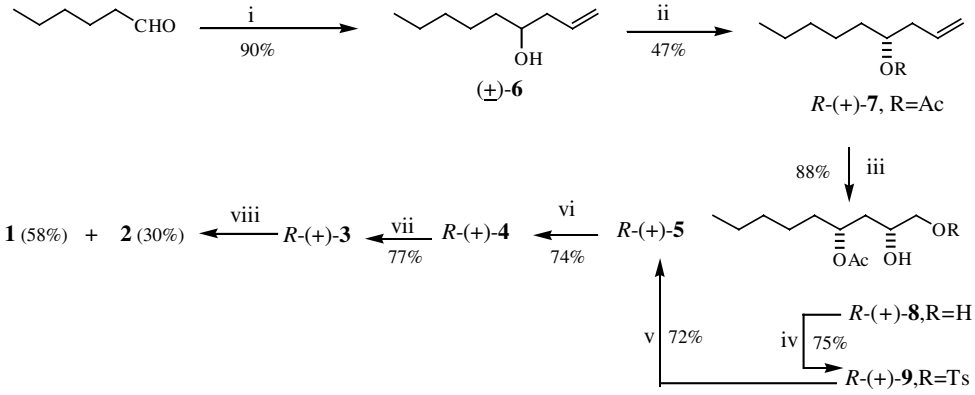


Scheme 2.

with the desired stereochemistry can be generated via a three-step protocol involving asymmetric dihydroxylation,[6] monotosylation[7] of the primary alcohol and subsequent epoxide[8] formation under the influence of a suitable base. We envisioned that the desired '*R*' stereochemistry of the free alcohol group could be generated by lipase-catalyzed transesterification[9] of the corresponding homoallylic precursor formed by a Barbier–Grignard reaction.[10] The synthetic approach to verbalactone is outlined in Scheme 3.

Treatment of the allyl zinc reagent prepared in situ from allyl bromide and zinc in THF and aq NH_4Cl with hexanal afforded the homoallylic alcohol (±)-**6** in 90% yield. The homoallylic acetate *R*-(+)-**7** possessing the same absolute configuration at C-12 as found in verbalactone **1** was prepared by transesterification of (±)-**6** with Amano lipase from *Pseudomonas fluorescens*, giving *R*-(+)-**7** in 47% yield and with an enantiomeric excess[11](ee) of 94% as determined by chiral HPLC analyses of the 3,5-dinitrobenzoate derivative. Next asymmetric dihydroxylation of *R*-(+)-**7** was effected using the ligand $(DHQD)_2PHAL$ to give a diastereoisomeric mixture of **8** in a diastereoisomeric ratio of 85:15[12] (from ^1H NMR). The required isomer *R*-(+)-**8** was separated from the diastereoisomeric mixture by preparative TLC in 88% yield and with 95% ee (determined by NMR spectroscopy using the chiral shift reagent $Eu(hfc)_3$)[13] and was monotosylated using TsCl and pyridine in CH_2Cl_2 at room temperature whereby hydroxy tosylate *R*-(+)-**9** was obtained in 75% yield. Tosylate *R*-(+)-**9** was converted into the epoxide *R*-(+)-**5** in 72% yield by treatment with 2 M NaOH in a 1:1 water–ether mixture at rt. Treatment of *R*-(+)-**5** with NaCN and $MgSO_4$ in refluxing dry methanol gave cyanoalcohol *R*-(+)-**4** in 74% yield. It was observed that during this step the acetate group in *R*-(+)-**4** was hydrolyzed under the reaction conditions. Completion of the synthesis required hydrolysis[14] of the cyanoalcohol *R*-(+)-**4**, which was carried out using a 25% methanolic solution of NaOH followed by acidic work-up (pH 5) with hydrochloric acid to give **3** in 77% yield. The pH during hydrolysis had to be carefully controlled as formation of the monomeric lactone **2** (62% yield, 94% ee) was observed at pH 2, as confirmed by IR, NMR and mass spectroscopy data, which were identical with those reported.[3]



Scheme 3. Reagents and conditions: (i) allyl bromide, Zn, THF, aq NH_4Cl, rt, 1 h (90%); (ii) Amano Lipase from *Pseudomonas fluorescens*, hexane, rt, 26 h (47%); (iii) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, *t*-BuOH–water (1:1), 0 °C, 24 h (88%); (iv) TsCl/Py, CH_2Cl_2, rt, 27 h (75%); (v) NaOH (2 M soln in water), Et_2O, 15 h, rt. (72%); (vi) $MgSO_4{\cdot}7H_2O$, NaCN, dry MeOH, reflux, 6 h (74%); (vii) aqueous NaOH (25%), MeOH, reflux, 1 M aq HCl (pH 5) (77%); (viii) (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 1.5 h; (b) DMAP (20 equiv), toluene, reflux, 4 h (58%).

In the next and final step, lactonization of 2 moles of **3** to give the dimeric lactone **1** was successfully achieved by Yamaguchi's method[15] in 58% yield and with >95% ee, the spectroscopic data[16] of which were identical with those of the natural product. In this step, a small amount of the monomeric lactone **2** (30%) was formed. No lactone formation took place at 3-OH perhaps due to ring strain effects or steric effects.

In conclusion, we have completed the first total synthesis of the macrocyclic dimeric lactone, verbalactone in a regioselective manner in 5.2% overall yield from hexanal. The desired stereochemistry was generated by kinetic resolution of a homoallylic alcohol and a Sharpless asymmetric dihydroxylation reaction.

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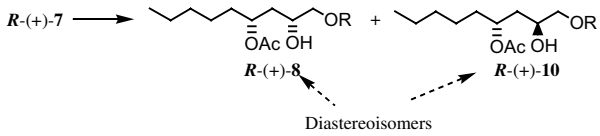
References and notes

1. Magiatis, P.; Spanakis, D.; Mitaku, S.; Tsitsa, E.; Mentis, A.; Harvala, C. *J. Nat. Prod.* **2001**, *64*, 1093–1094.
2. Doshida, J.; Hasegawa, H.; Onuki, H.; Shimidzu, N. *J. Antibiot.* **1996**, *49*, 1105–1109.
3. Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335–3346.
4. (a) Bez, G.; Saikia, A. K.; Kalita, D.; Bezbarua, M. S.; Barua, N. C. *Ind. J. Chem.* **1998**, *37B*, 325–328; (b) Kalita, D.; Khan, A. T.; Saikia, A. K.; Barua, N. C. *Synthesis* **1998**, 975–976; (c) Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron* **1999**, *55*, 5177–5184.
5. (a) Smith, J. G. *Synthesis* **1984**, 629–656; (b) Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039–2051; (c) Kalita, B.; Barua, N. C.; Bezbarua, M.; Bez, G. *Synlett* **2001**, 1411–1414; (d) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209–6212; (e) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1990**, *55*, 2016–2018.
6. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Orikawa, K.; Ang, Z.-M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768–2771; (b) Pandey, R. K.; Fernandes, R. A.; Kumer, P. *Tetrahedron Lett.* **2002**, *43*, 4425–4426.
7. (a) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957–1959; (b) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *65*, 2869–2875.
8. Cho, B. T.; Yang, W. K.; Choi, O. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1204–1211.
9. (a) Sing, S.; Kumar, S.; Chimni, S. S. *Synlett* **2002**, *8*, 1277–1280; (b) Mandai, T.; Oshitari, T.; Susowake, M. *Synlett* **2002**, 1665–1668.
10. (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodriguez, R. A. *J. Org. Chem.* **2001**, *66*, 5208–5216; (b) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589–8594; (c) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087–3091.
11. The enantiomeric excess (ee) of *R*-(+)-**7** was determined by chiral HPLC analyses using a Daicel CHIRALCEL OD column (250 mm × 4.6 mm, eluent: hexane–*i*PrOH) after conversion to the corresponding 3,5-dinitrobenzoate. Conversion of *R*-(+)-**7** to the corresponding 3,5-dinitrobenzoate was carried out by saponification followed by esterification.
12. During the Sharpless asymmetric dihydroxylation step, diastereoisomers were formed.



The diastereoisomeric ratio was determined as 85:15 by ^{1}H NMR (500 MHz) spectroscopic analyses of the crude product mixture.
13. The ee's of *R*-(+)-**8**, **2** and **1** were determined by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$.
14. (a) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967–7974; (b) Fernandes, R. A.; Kumer, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349–4356.
15. (a) Yamaguchi, M.; Inanaga, J.; Hirata, K.; Sacki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; (b) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, 215–228.
16. Spectroscopic data: data for compound **1**: $[\alpha]_D^{25}$ +6.2 (*c* 0.9, $CHCl_3$) [lit.[1] $[\alpha]_D^{25}$ +7.3 (*c* 0.9, $CHCl_3$)]; ^{1}H NMR δ_H (500 MHz, $CDCl_3$): 4.90–4.95 (2H, ddd, $J = 9.9$, 4.7, 4.5 Hz, H-6, 12), 4.05–4.08 (2H, ddd, $J = 4.5$, 3.8, 3.2 Hz, H-4, 10), 3.51–3.65 (2H, br, 3-OH, 10-OH), 2.41–2.86 (4H, d, $J = 3.5$ Hz, H-3, 9), 2.03–2.10 (2H, ddd, $J = 14.5$, 9.5, 3.1 Hz, H-5b, 11b), 1.96 (2H, td, $J = 15$, 4.5 Hz, H-5a, 11a), 1.49–1.57 (4H, m, H-13, 18), 1.22–1.29 (12H, m, H-14, 15, 16, 19, 20, 21), 0.85–0.87 (6H, t, $J = 7.5$ Hz, H-17, 22); ^{13}C NMR δ_C (125 MHz, $CDCl_3$): 172.9 (C-2, 8), 72.5 (C-6, 12), 64.5 (C-4, 10), 39.4 (C-3, 9), 36.9 (C-5, 11), 31.5 (C-13, 18), 31.3 (C-15, 20), 24.4 (C-14, 19), 22.4 (C-16, 21), 13.9 (C-17, 22); IR ν_{max}: 3520, 1712, 1269, 1172 cm^{-1}; MS(ESI): m/z 395.2 ($[M + Na]^+$). Data for **2**: $[\alpha]_D^{25}$ +18 (*c* 0.9, $CHCl_3$) [lit.[3] $[\alpha]_D^{20}$ +36.9 (*c* 0.92, CH_2Cl_2)]; ^{1}H NMR δ_H (500 MHz, $CDCl_3$): 4.62–4.68 (1H, dddd, $J = 10.5$, 7.5, 4.8, 4.2 Hz, 5-H_{ax}), 4.30–4.38 (1H, dddd $J = 5$, 4.1, 3.9, 3.6 Hz, 3-H_{eq}), 2.69–2.73 (1H, dd, $J = 17$, 5.5 Hz, 2-H_{ax}), 2.57–2.62 (1H, ddd, $J = 17$, 4.2, 3 Hz, 2-H_{eq}), 2.07–2.12 (1H, br, 3-OH_{ax}), 1.94–1.96 (1H, dddd, $J = 13.5$, 4.5, 3.5, 2.2 Hz, 4-H_{eq}), 1.73–1.74 (1H, ddd, $J = 13.5$, 10.3, 4.2 Hz, 4-H_{ax}), 1.56–1.76 (2H, m, H-6), 1.34–1.55 (2H, m, H-7), 1.31–1.34 (2H, m, H-8), 1.29–1.30 (2H, m, H-9), 0.86–0.89 (3H, t, $J = 7.2$ Hz, H-10); ^{13}C NMR δ_C (125 MHz, $CDCl_3$): 170.4 (C-1), 76.1 (C-5), 62.7 (C-3), 38.7 (C-2), 36 (C-4), 35.5 (C-6), 31.6 (C-8), 24.4 (C-7), 22.6 (C-9), 13.9 (C-10); IR ν_{max}: 3200–3600 (OH), 1739 (lactone).