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A stereoselective synthesis of verbalactone—determination of absolute stereochemistry☆

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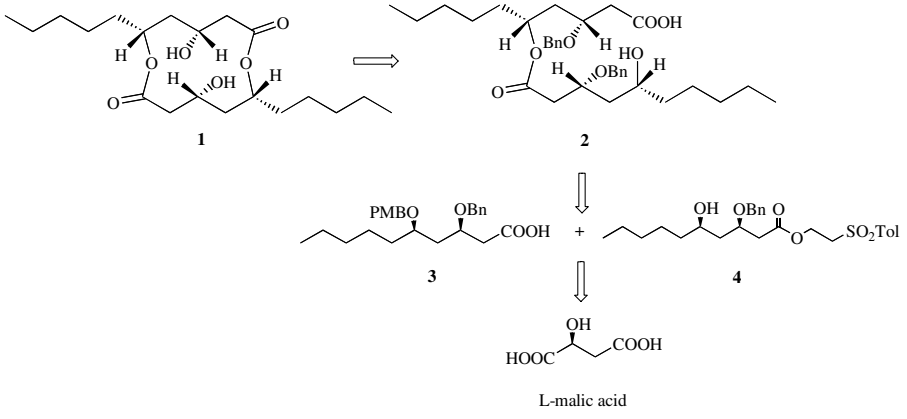
Abstract—A total synthesis of verbalactone has been achieved starting from L-malic acid. The two appropriately protected acid and alcohol segments were prepared from L-malic acid and lactonized under Yamaguchi conditions.

Verbalactone (**1**), a novel macrocyclic dimer lactone, was isolated from the roots of *Verbascum undulatum* and exhibited interesting antibacterial activity.[1] It was the first example where a 1,7-dioxacyclododecane moiety was reported as the ring system of a natural product. The structure and the absolute stereochemistry of **1** as 4*R*,6*R*,10*R*,12*R* was determined by spectral methods (1D and 2D NMR, MS) and chemical correlation. Verbalactone (**1**) is thus a dimeric lactone with C_2-symmetry and has a NMR profile similar to the monomer lactone of (3*R*,5*R*)-dihydroxydecanoic acid.[2] In continuation of our interest on the synthesis of natural lactones,[3] we herein report a stereoselective synthesis of verbalactone (**1**).

The retrosynthetic plan for **1** (Scheme 1) indicated that the *seco* acid **2** could be a late stage intermediate. Acid **2**, in turn, could be prepared by coupling **3** and **4** via an esterification, while **3** and **4** could be prepared from L-malic acid. Thus, the basic strategy for the synthesis of the key fragment **3** was to utilize the lone stereocenter in malic acid as C-5 and to introduce the C-3 hydroxyl of the target molecule by an asymmetric Sharpless epoxidation.



Scheme 1. Retrosynthetic analysis of verbalactone **1**.

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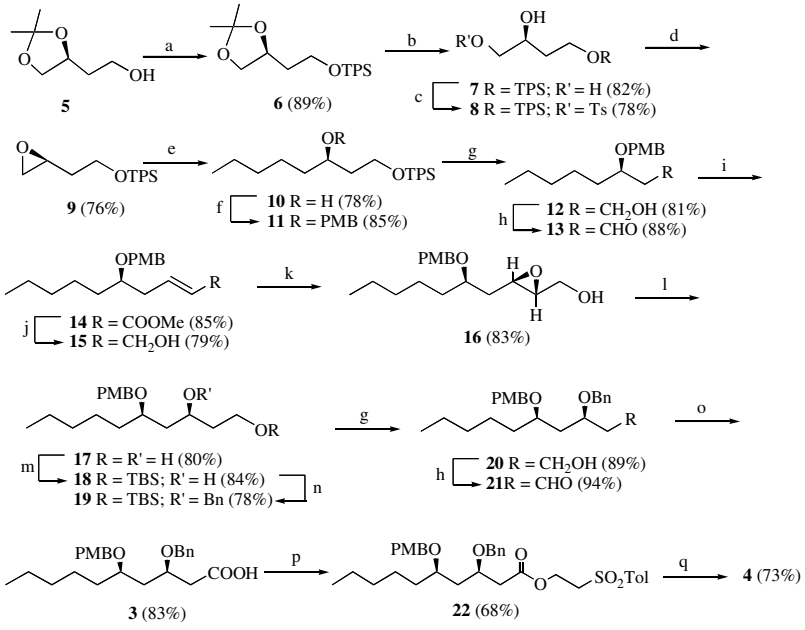
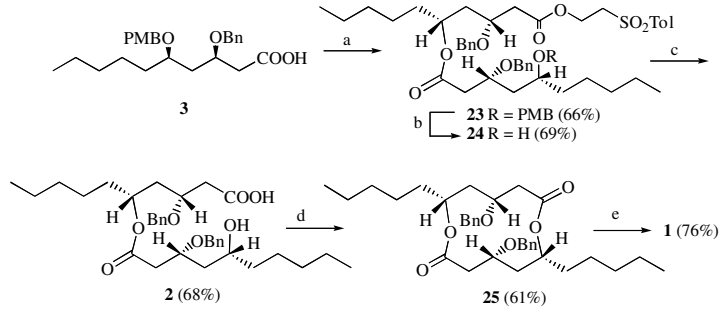
Accordingly, the known alcohol **5**[4] (Scheme 2), derived from L-malic acid, was silylated (TBDPSCl, imidazole, CH_2Cl_2) to give **6** (89%), which on hydrolysis (60% aq AcOH) gave the diol **7** (82%). Selective tosylation of **7** with *p*-TsCl and Et_3N in CH_2Cl_2 furnished **8** (78%), which was reacted with 2 equiv of K_2CO_3 in MeOH to give the epoxide **9** (76%). Selective opening of **9** with CuI and *n*-BuLi[5] furnished **10** in 78% yield (Scheme 2), which on protection with PMBBr gave **11** in 85% yield. Desilylation of **11** with TBAF gave alcohol **12** (81%), which on oxidation under Swern conditions and homologation of **13** with (methoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux afforded ester **14** in 85% yield. Reduction of **14** using DIBAL-H furnished the alcohol **15** (79%), which on Sharpless asymmetric epoxidation[6] with cumene hydroperoxide, (−)-DIPT and Ti(O*i*-Pr)$_4$ exclusively gave the epoxide **16** in 83% yield. Regioselective reductive opening of **16** with $NaAlH_2(OCH_2CH_2OMe)_2$[7] gave the 1,3-diol **17** in 80% yield. Silylation (TBDMSCl, imidazole, CH_2Cl_2) of **17** and subsequent benzylation of the secondary alcohol in **18** using NaH and BnBr gave **19** (78%). Deprotection of the TBDMS ether in **19** with TBAF and subsequent oxidation of **20** under Swern conditions furnished the corresponding aldehyde **21** (94%), which on further oxidation using $NaClO_2$[8] and 30% H_2O_2 in *t*-BuOH/H_2O (2:1) gave **3** in 83% yield.

Having completed a synthesis of the key fragment **3**, it was subjected to esterification with *p*-toluenesulfonylethanol via the mixed anhydride prepared on reaction of **3** with 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) in the presence of DMAP to afford ester **22** (68%). Since the cleavage of *p*-toluenesulfonylethyl groups with DBN[3,9] is very facile and highly selective and does not effect other ester groups, it was thus chosen for the



Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 5 h; (b) 60% aq AcOH, rt, 12 h; (c) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 10 h; (d) K_2CO_3, MeOH, rt, 2 h; (e) CuI, *n*-BuLi, dry ether, 0 °C, 2 h; (f) PMBBr, NaH, THF, 0 °C—rt, 5 h; (g) TBAF, CH_2Cl_2, rt, 10 h; (h) $(COCl)_2$ DMSO, Et_3N, CH_2Cl_2, −78 °C, 3 h; (i) $Ph_3P{=}CHCOOMe$, benzene, reflux, 2 h; (j) DIBAL-H, CH_2Cl_2, rt, 3 h; (k) (−)-DIPT, Ti(O*i*-Pr)$_4$ cumene hydroperoxide, 4 Å—MS, CH_2Cl_2, −20 °C, 3 h; (l) $NaAlH_2(OCH_2CH_2OMe)_2$, THF, 0 °C, 5 h; (m) TBDMSCl, imidazole, CH_2Cl_2 rt, 6 h; (n) BnBr, NaH, THF, 0 °C—rt, 4 h; (o) $NaClO_2$, 30% H_2O_2, *t*-BuOH/H_2O (2:1), 0 °C—rt, 10 h; (p) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, $HOCH_2CH_2SO_2Ar$, DMAP, toluene, rt, 16 h; (q) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C—rt, 5 h.



Scheme 3. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, **4**, DMAP, toluene, rt, 20 h; (b) DDQ, CH_2Cl_2/H_2O (19:1), rt, 3 h; (c) DBN, benzene, rt, 12 h; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, 90 °C, 24 h; (e) $TiCl_4$, CH_2Cl_2, 0 °C, 1 h.

protection of acid **3**, in the present synthesis. Oxidative deprotection of the PMB group in **22** using DDQ in aq CH_2Cl_2 gave the hydroxy ester **4** in 73% yield, ready for coupling with segment **3**.

Esterification of acid **3** with alcohol **4** under Yamaguchi conditions gave **23** (66%), which on PMB deprotection furnished **24** in 69% yield (Scheme 3). Selective cleavage of the *p*-toluenesulfonylethyl group in **24** was effected with DBN in C_6H_6 to give seco acid **2** (68%), which on lactonization under Yamaguchi conditions[10] (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene) afforded **25** in 61% yield. Finally, deprotection of the benzyl groups in **24** was effected with $TiCl_4$ (1 equiv) in CH_2Cl_2 at 0 °C to give synthetic **1** as a colorless oil in 76% yield, $[\alpha]_D^{25} + 8.2$ (*c* 0.3, $CHCl_3$). The ^1H and ^{13}C NMR data and optical rotation value of synthetic **1**[11] were in good accordance with those of the natural product.[1]

In conclusion, a synthesis of verbalactone (**1**) by a combination of chiral pool and asymmetric approaches has been achieved.

Acknowledgements

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11. Spectral data of verbalactone (**1**): Colorless oil, $[\alpha]_D^{25}$ +8.2 (*c* 0.3, $CHCl_3$); lit.[1] $[\alpha]_D^{25} + 7.3$ (*c* 0.9, $CHCl_3$); IR (neat): 3518, 1710, 1265, 1170 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, 6H, *J* = 7.0 Hz, H-17, 22), 1.22–1.31 (m, 12H, H-14, 15, 16,19, 20, 21), 1.49–1.55 (m, 4H, H-13, 18), 1.96 (td, 2H, *J* = 15.2, 4.2 Hz, H-5a, 11a), 2.05 (ddd, 2H, *J* = 15.2, 10.2, 3.1 Hz, H-5b, 11b), 2.68 (d, 4H, *J* = 3.6 Hz, H-3, 9), 3.73 (br s, 2H, 3-OH, 10-OH), 4.06 (ddd, 2H, *J* = 4.2, 3.6, 3.1 Hz, H-4, 10), 4.94 (ddd, 2H, *J* = 10.2, 4.7, 4.6 Hz, H-6, 12); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 13.91, 22.45, 25.52, 31.42, 31.78, 38.24, 39.29, 64.97, 72.57, 172.91; FAB MS (*m*/*z*, %): 373 (M^++1, 32), 187 (94), 151 (26), 127 (100), 93 (34), 55 (44).