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TOTAL SYNTHESIS OF THE UNUSUAL CYCLOSPORINE AMINO ACID MeBMT

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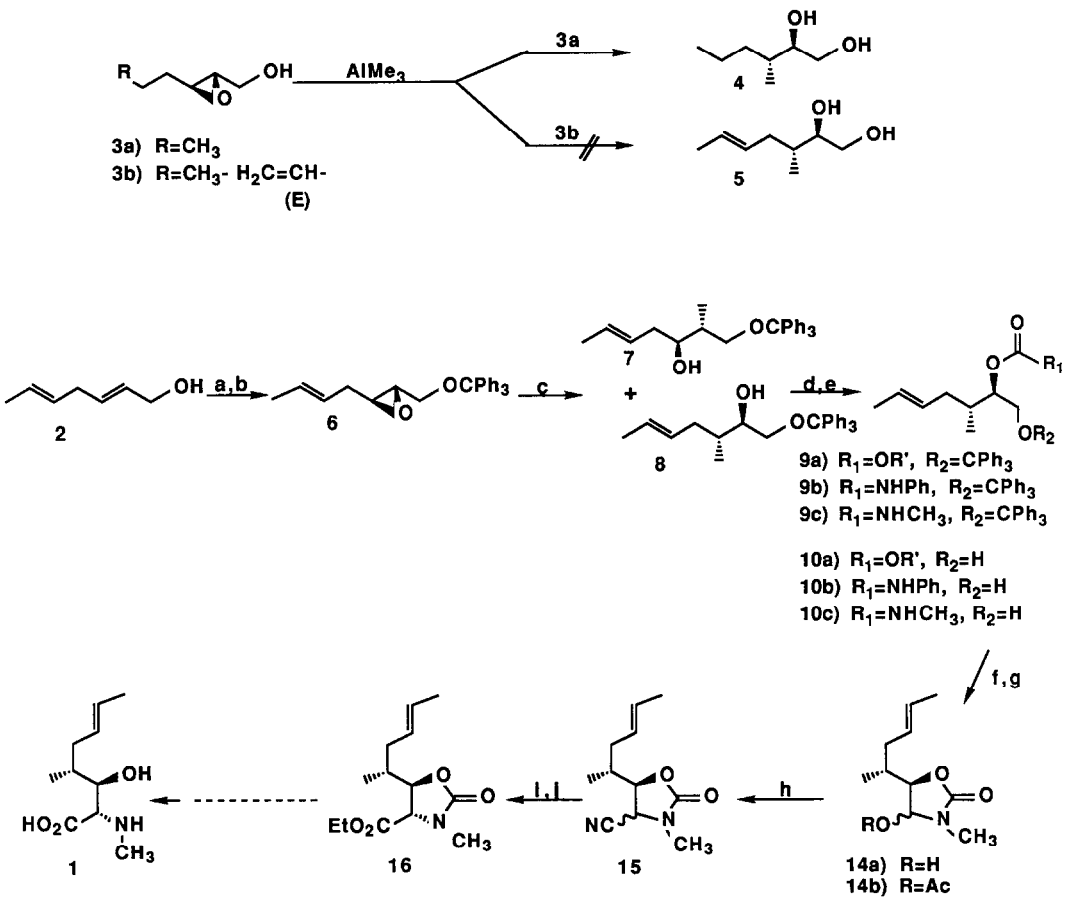
Summary: Sharpless epoxidation of the readily available dienol 2, followed by regiospecific opening with $Me_2CuLi/BF_3{\cdot}Et_2O$ yields, after protecting group manipulation, the mono-protected diol 10c. Swern oxidation gives the cyclic carbaminol 14a which is easily manipulated to α-cyano oxazolidinone 15 and thus, by literature methods, to the title compound. Using this procedure, good overall yield and high enantiomeric purity are obtained.

In connection with our efforts to synthesize and elucidate the structure-activity relationships of the cyclosporines,[1,2] we need large quantities of the unusual amino acid "MeBMT" (1). This β-OH α-amino acid, which appears necessary for full activity of the cyclosporines,[2b] presents a synthetic challenge with its three contiguous asymmetric centers and trans-olefinic functionality. Two synthetic routes to 1 have been recently published;[3,4] in this communication, we disclose preliminary results of a new route which can provide convenient access to 1 in large quantities.

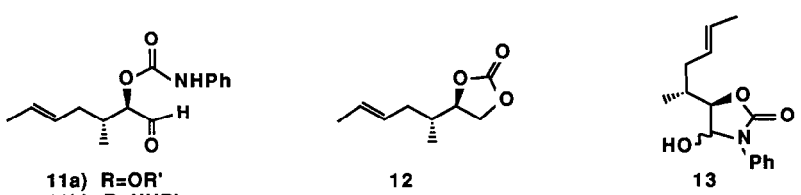
Initially, we had envisaged "cutting into" Wenger's[3] synthesis approximately half-way through his (twenty four step) route, by means of Sharpless epoxidation[5] on the readily available[6,7] dienol 2, followed by regiospecific methylation with $AlMe_3$.[8,9] thus setting the key stereochemistry at C2 (OH) and C3 (CH_3). Using compound 3a[10] as a model system, the desired diol was in fact produced in 80-90% yield as a single regioisomer.[11] However, when 3b (from 2: 2.2 eq. ^tBuOOH, 0.08 eq. $Ti(O^iPr)_4$, 0.1 eq. L-DET, 5.5 h, 81%) was used, formation of a complex mixture occurred wherein the desired 5 was observed only as a minor product.

With direct methylation unavailable to us, we next attempted use of a bulky O-protecting group to effect regiospecificity in a cuprate opening. Introduction of the trityl ether, which appeared to be the protecting group of choice,[12] proceeded readily to yield 6 in 94% yield.[13] To our initial dismay, however, a variety of lower and higher order, homo- and hetero- cuprates gave compounds 7 and 8 in ratios ranging from 1:1 to 1.5:1 favoring the undesired 1,3-diol derivative 7. Useful ratios were finally obtained by the addition of $BF_3{\cdot}Et_2O$;[14] thus, 2 eq. each of Me_2CuLi and $BF_3{\cdot}Et_2O$ (Et_2O, -75° 20-30 min) yielded 7 and 8 in an 15:85 ratio with 94% conversion (8: $[\alpha]_D$-15.4°, c 1.0, $CHCl_3$).

We had then planned to protect the C2 alcohol as a carbonate (9a), followed by C1 deprotection, oxidation to the aldehyde (11a), and a Strecker amino nitrile synthesis, analogous to that used by Wenger[3]. Intramolecular ring closure would then yield oxazolidinone 15, which would be converted to MeBMT by the literature method. Reaction



a) 2.2 eq. ^{t}BuOOH, 0.08 eq. $Ti(O^{i}Pr)_4$, 0.1 eq. L-DET, -20°, 4 h, 81%; b) 1.1 eq. Ph_3CCl, 1.2 eq. DBU, 0° to room temp, 7 h, 94%; c) 2 eq. Me_2CuLi, 2 eq. $BF_3.Et_2O$, -75°C, 20-30 min, 14% 7, 80% 8; d)(to 9c) MeNCO, $PhCH_3$, 110° (sealed tube); e)(to 10a) 0.1 eq. ^{p}TsOH H_2O, MeOH, 16 h, 64% from 8; f)(to 14a)1.5 eq.$(COCl)_2$, 1.15 eq. DMSO, -40°, 15 min, then 5 eq. NEt_3; g)(to 14b) 1.25 eq. Ac_20 (in situ), room temp, 15 h, 83%from 10; h) 3 eq. TMSiCN, cat. $BF_3.Et_2O$, $MeNO_2$, 25 min, room temp, 97%; i) 2 eq. K_2CO_3, 95% EtOH, 9 h, room temp, 88%; j) 1.3 eq. HCl, 95% EtOH, 2.25 h, room temp, 72%.



of alcohol 8 with various chloroformates was poor, though, and furthermore the resultant carbonates cyclized to 12 upon C1 deprotection. Reaction of 8 with phenyl isocyanate to give 9b was considerably more successful. However, deprotection and oxidation of the C1 alcohol gave the cyclic 13 (IR: 1745 cm^{-1}, NMR: H (C1) br m, δ 5.42 ppm) in good yield, rather than the expected open chain 11b.[15] At this point we realized that if conversion of the carbaminol hydroxyl to a carboxylate could be effected, this result might be highly useful, whereby the carbamate "protecting group" would act as the eventual progenitor of the desired methylamino functionality.

Accordingly, protection of 8 as the methyl carbamate (9c: mp 125-127.5° from cyclohexane; $[\alpha]_D$ +6.5°, c 1.0, EtOH) was carried out, followed by removal of the trityl group, to yield 10c (mp 60.5-62° from cyclohexane; $[\alpha_D]$ +31.5°, c1.0, $CHCl_3$) in 64% overall yield. Swern oxidation[16] followed by in situ acetylation (1.25 eq. Ac_2O, 16 h at room temp.), then gave the oily acetate 14b as a ca. 1:1 mixture of diastereomers in 83% yield from 10c.[17] Reaction of 14b with TMSCN in the presence of catalytic $BF_3 \cdot Et_2O$ in nitromethane[18] gave the desired 15 as a ca. 1.6:1 ratio of cis:trans isomers (relative to the oxazolidinone ring) in excellent yield.[19] Compound 4 was converted to the carboethoxy oxazolidinone 16 by the literature method.[3,20] The optical rotation of the material thus obtained ($[\alpha]_D$ +27.6°, c 1.0, $CHCl_3$ vs. lit.[3] $[\alpha]_D$ +29.5°, c 1.0, $CHCl_3$) indicated an e.e. of 94%, which should be suitable for virtually all uses. Enantiomerically pure material is obtained, if desired, by conversion to the free acid and crystallization with (+)-ephedrine.[21]

This synthetic route provides a convenient method for obtaining MeBMT in quantity, with a minimum of steps requiring chromatographic purification. Full experimental details for scaleup to multigram quantities and applications to the synthesis of novel analogs of 1 will be reported in due course.

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7) In earlier runs, a persistent impurity later identified as the 1,4-addition product of propargyl alcohol dianion to the crotyl bromide was carried through the first several steps. This regioisomer was removed at the stage of ring opening (9 to 10). Isomerically pure 6 may be obtained by more careful distillation of the precursor ynenol (c.f. ref. 7); however our currently preferred approach is to carry the mixture of compounds through to the stage of methyl carbamate 10b, then purify it by recrystallization.

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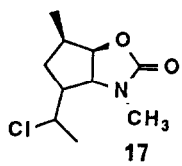
19) Direct conversion of 11 to 13 was possible by this method; however, yields were considerably lower (ca. 20%).
20) In our hands, complete epimerization to the desired "trans" (4S, 5R) oxazolidinone does not take place under the literature conditions, a ca. 8:1 ratio of (easily separated) trans:cis being obtained instead. We are currently exploring methods for obtaining the "trans" compound exclusively.
21) Aebi, J. and Rich, D. H. Unpublished observations.



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