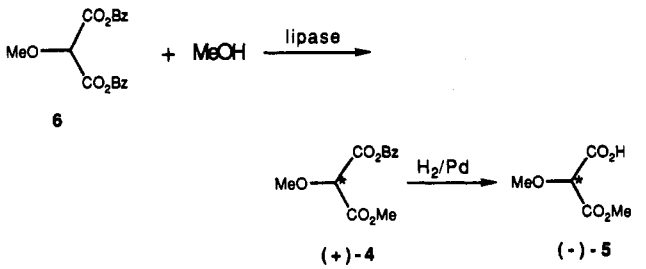
Scheme II



firmed by carrying out the reaction with benzyl alcohol in the presence of an equimolar amount of methanol, in which case the reaction reached equilibrium at 20% conversion.

In a further preparative experiment, we showed that it is possible to carry out a stereoselective enzymatic transesterification with methanol as well. Thus, when the corresponding methoxy-substituted dibenzyl malonate 6 was subjected to the lipase from *Candida cylindracea* and methanol, under similar conditions, transesterification occured at a similar rate and the mixed methyl benzyl ester was formed. Determination of optical purity by polarimetry and HPLC on a chiral column revealed that in this case the opposite (+)-4 enantiomer was formed with an ee value of 90–95%.[10] Hydrogenolysis of this material would give the respective (-) enantiomer of the half ester 5 (Scheme II). The prochiral specificity of the enzyme thus allows the preparation of either the (+) or (-) enantiomer of the mixed diesters of monosubstituted malonates by following one of the two complementary routes.

This study significantly extends the synthetic utility of lipases in organic solvents. It provided the first synthetic route to chiral monosubstituted malonates and points the way to the synthesis of other analogues of this important class of compounds. Further work in this field is currently underway in our laboratory.

Acknowledgment. We thank Dr. A. Kirby for useful discussions and the Israel Academy of Sciences and Humanities for financial support.

Supplementary Material Available: Experimental details and ^{1}H NMR for obtained compounds (12 pages). Ordering information is given on any current masthead page.

(10) This ee value was obtained when the reaction proceeded to 50%. In this case the slowdown toward 70% conversion was accompanied by significant formation of the byproduct dimethyl ester with a concomittant lower optical purity for (+)-4.

Pyranose α-Enones Provide Ready Access to Functionalized *trans*-Decalins via Bis-Annulated Pyranosides Obtained by Intramolecular Diels–Alder Reactions. A Key Intermediate for Forskolin[1]

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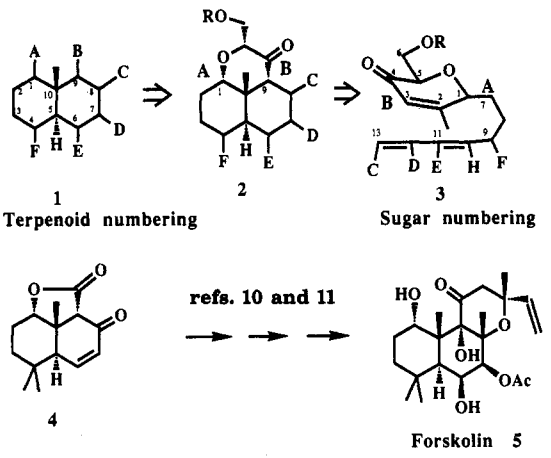
Summary: Intramolecular Diels–Alder routes for the preparation of bis-annulated pyranosides, as chiral precursors of functionalized *trans*-decalin rings of terpenoid natural products, have been investigated.

Strategies for the use of carbohydrate derivatives to synthesize carbocyclic natural products in our laboratory have exploited the sugar ring both for its stereodirecting properties and reactivity as well as for the variety of latent functional groups that it masks.[2] The sugar therefore serves as more than a source of chirality, and for maximum utility, the integrity of the ring needs to be maintained as far into the synthesis as possible. This approach was illustrated in the synthesis of *N*-acetyl actinobolamine[3] where the enhanced Diels–Alder reactivity of a carbohydrate-derived α-enone vis-a-vis its carbocyclic counterpart[4] was used to furnish the molecular framework. Our recent successes with tricothecanes,[5] pipitzol,[6] polyquinanes,[7] and phyllantocin[8] have encouraged us to consider other carbocyclic targets, and *trans*-decalin core 1, common to many terpenoids, is the topic of this manuscript.

Scheme I



The labels A → F in 1 (Scheme I) represent sites at which functional groups and/or other rings are frequently located on the bicyclic core. In view of the aforementioned high reactivity of carbohydrate derived α-enones, an intramolecular Diels–Alder (IMDA) reaction[9] seemed an attractive avenue to 1. Accordingly retrosynthetic analysis led to the bis-annulated pyranose 2 and thence to the hex-2-en-4-ulopyrano intermediate 3. In this manuscript we demonstrate the validity of this approach with a syn-

(1) This work was supported by grants from NIH (GM 37380) and NSF (8920033).

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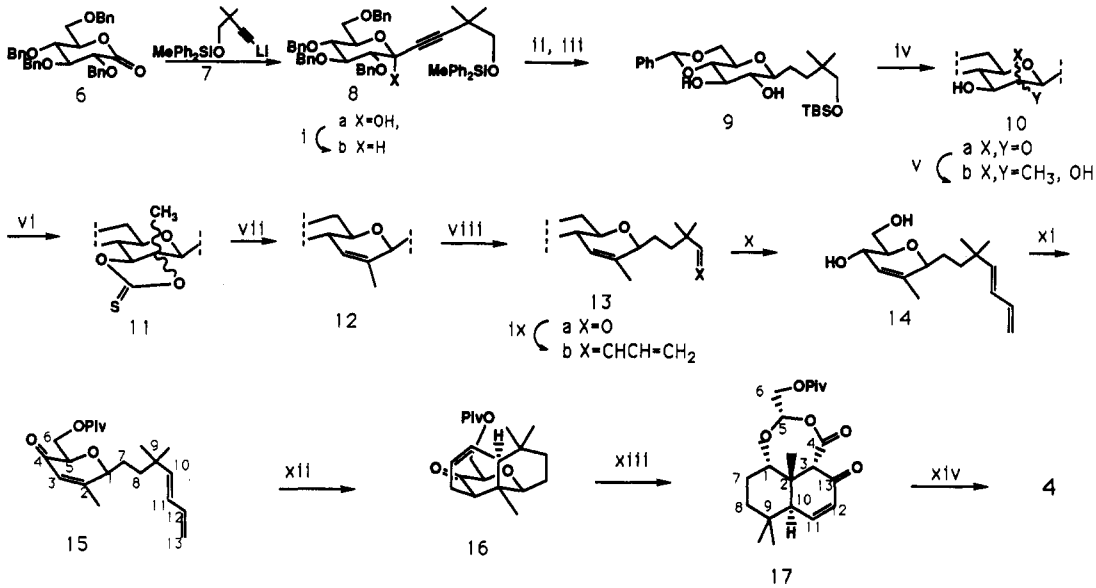
Scheme II[a]



[a] (i) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (55% from 6); (ii) H_2, Pd/C, MeOH, $HClO_4$, then $PhCHBr_2$, Py (iii), TBSCl, Py, DMAP, CH_2Cl_2 (76% from 8); (iv) nBu_2SnO, $PhCH_3$, then Br_2/CCl_4 (72%); (v) MeMgBr/THF (82%); (vi) NaH, nBu_4NI, CS_2, CH_3I; (vii) $(MeO)_3P$ (63% from 11); (viii) TBAF, THF then PCC (65%); (ix) $CH_2{=}CHCH_2MgBr$ then $POCl_3$, Py (64%); (x) CSA, MeOH (85%); (xi) Me_3CCOCl, Py, DMAP, CH_2Cl_2, then PCC (50%); (xii) hydroquinone, xylene, reflux (75%); (xiii) Na_2CrO_4, Ac_2O/AcOH; (xiv) NaOMe/MeOH (67% from 16).

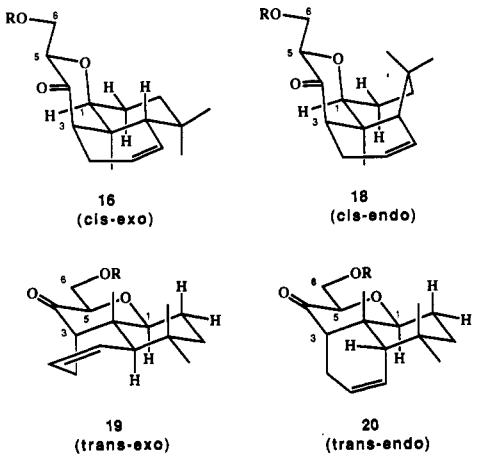
thesis of the *trans*-decalin 4, the racemic version of which has been prepared by Ruveda and co-workers[10] as an advanced intermediate to forskolin,[11] 5.

The IMDA transition state[12] which is needed to obtain the desired ring junction shown in 2 could conceivably arise from either the α or β anomer of 3. However, judging from results of additions to hex-2-enopyranosides,[13-15] approach from the α-face (i.e., below the ring) is stereoelectronically disfavored. Hence, only β configuration for the diene-bearing appendage was considered.

The strategy for establishing the β-*C*-glycosyl linkage was based on the aldose reduction process introduced independently by Gray[16] and Kishi.[17] Accordingly the hemiketal, **8a**, obtained by reaction of the alkynyl lithium 7 with the known lactone **6**,[18] was reduced with triethylsilane to give the β-D-*C*-glycoside **8b**. Exhaustive hydrogenation/hydrogenolysis led to a pentol which upon benzylidination and silylation afforded diol **9**.

Initial attempts to install the vinyl-CH_3 using a procedure developed by us[19] and improved by Parker[20] were unsuccessful and so the alternative, shown in Scheme II, was implemented. Chemoselective oxidation at C2 was achieved by the Hanessian–David[21] procedure involving

Chart I



in situ reaction of the stannylene derivative of **9** with bromine. The resulting ketone, **10a**, upon treatment with methylmagnesium bromide led to the epimeric tertiary alcohols **10b**, both epimers of which were smoothly converted into the cyclic thionocarbonate mixture **11**. Reduction with trimethyl phosphite, according with the Corey–Winter procedure,[22] afforded the alkene **12**.

Elaboration of the diene component involved addition of allylmagnesium bromide to aldehyde **13a** followed by dehydration to **13b**, and the benzylidene ring was then cleaved by treatment with acidified methanol. Pivaloylation of the resulting diol, **14**, followed by oxidation then gave the desired Diels–Alder precursor **15**, which upon reflux in xylene for 48 h afforded unchanged starting material and a single IMDA product in 2:1 ratio. The ^1H NMR spectrum of the product showed H1 as a slightly broadened singlet. The four possible structures from the reaction are presented in Chart I, the transition-state alignments[12] being shown in parentheses. Compounds **19** and **20** can be eliminated because H1 would exist as double doublets, $J \approx 4$ and 10 Hz, in view of the vicinal cis and

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trans couplings, rather than as the observed broadened singlet. This requirement, which implies cis couplings, could be met by either **16** or the more highly strained isomer **18**. Subsequent transformations, now described, eliminate the latter.

Ketopyranoses such as **16** can be conveniently degraded by Baeyer–Villiger oxidation using *m*-CPBA,[23] oxygen being inserted chemoselectively into the electron rich C4–C5 bond. Sodium chromate[24] achieved a similar result with accompanying with allylic oxidation to give the α-enone **17**. Upon methanolysis the acylal function was cleaved leading to lactone **4** whose ^{1}H NMR data were identical to those described by Ruveda[10b] for the racemic modification.

Use of the above strategy for various synthetic targets is underway and will be described in due course.

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Asymmetric Synthesis of Macbecin I

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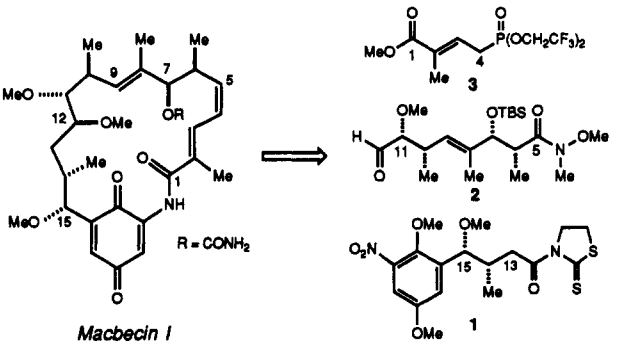
Received November 7, 1991

Summary: The asymmetric synthesis of macbecin I is described wherein the absolute stereochemical relationships were established through the use of chiral boron aldol bond constructions and internally directed α-methoxy ketone reduction, while the *E,Z* dienic amide moiety was installed in one step using a vinylogous phosphonate reagent.

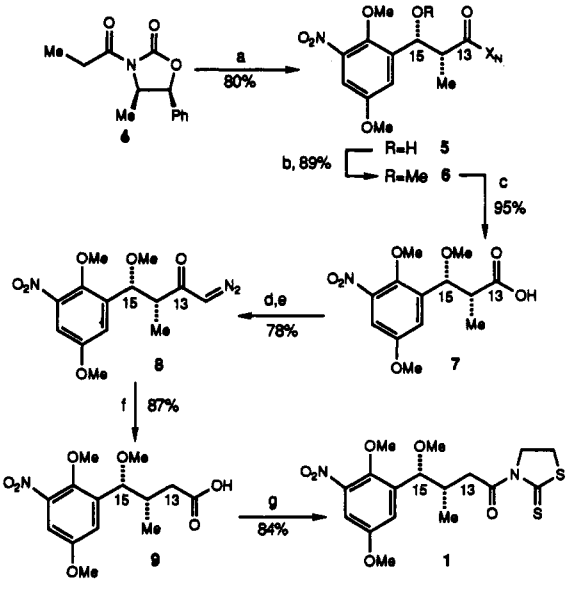
The benzoquinoid antibiotics, the macbecins,[1] herbimycins,[2] and geldanamycin,[3] are representatives of an emerging class of ansa-bridged macrocyclic lactams possessing a significant range of antitumor activity.[4] We describe in this paper our studies culminating in the successful total synthesis of macbecin I. Our retrosynthetic analysis is shown in Scheme I. Both the structural complexity and the promising antitumor potential of these molecules have made them attractive as targets for total synthesis. To date, one total synthesis of macbecin I[5] and one of herbimycin A have appeared.[6]

The synthesis of **1** was initiated with the C_{14}–C_{15} aldol bond construction that establishes the two stereogenic centers resident in the fragment (Scheme II). Treatment of the (*Z*)-boron enolate of imide **4**,[7] derived from the (4*R*,5*S*)-norephedrine-based oxazolidinone (X_NH), with 2,5-dimethoxy-3-nitrobenzaldehyde[8] according to the standard conditions[9] afforded the desired aldol adduct **5** (80%, >97% diastereomeric purity).[10] Methylation of the C_{15}-hydroxyl was accomplished by reaction of the aldol adduct with trimethyloxonium tetrafluoroborate (Proton Sponge, CH_2Cl_2, 25 °C, 5 days).[11] Subsequently, a one-carbon homologation was effected using the Arndt–Eistert sequence.[12] Thus, imide **6** was treated with lithium hy-

Scheme I



Scheme II[a]



[a] Key: (a) *n*-Bu_2BOTf, Et_3N, 2,5-dimethoxy-3-nitrobenzaldehyde; (b) Me_3O BF_4, Proton Sponge, CH_2Cl_2, 25 °C; (c) LiOOH, THF/H_2O, 0 °C; (d) $(ClCO)_2$, DMF, CH_2Cl_2, 25 °C; (e) CH_2N_2, Et_2O/CH_2Cl_2, 0–25 °C; (f) $AgNO_3$, THF/H_2O, 25 °C; (g) 2-mercaptothiazoline, EDC, DMAP, CH_2Cl_2.

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