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DIASTEREOSELECTIVE π-FACIALLY CONTROLLED NUCLEOPHILIC ADDITIONS OF CHIRAL VINYLORGANOMETALLICS TO CHIRAL β,γ-UNSATURATED KETONES. 2. A PRACTICAL METHOD FOR STEREOCONTROLLED ELABORATION OF THE DECAHYDRO-as-INDACENE SUBUNIT OF IKARUGAMYCIN

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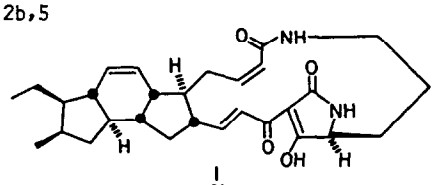
Summary: 7,7-Dimethoxy-5-norbornen-2-one has been converted in 7 steps to tricyclic enone **10**, which comprises a principal subunit of the ikarugamycin structure.

7,7-Dimethoxy-5-norbornen-2-one (**2**) has recently been found to capture chiral vinyl organometallic reagents with significant levels of intermolecular diastereoselection.[1] We now report an application of this kinetic resolution to a practical convergent synthesis of the tricyclic as-indacene moiety contained in the antibiotic ikarugamycin (**1**).[2] The protocol couples this carbonyl condensation with an anionic oxy-Cope rearrangement. The same target has received prior attention by two research groups,[3,4] both of which have chosen to adopt intramolecular Diels-Alder strategies in line with the existing biosynthetic hypothesis.[2b,5]



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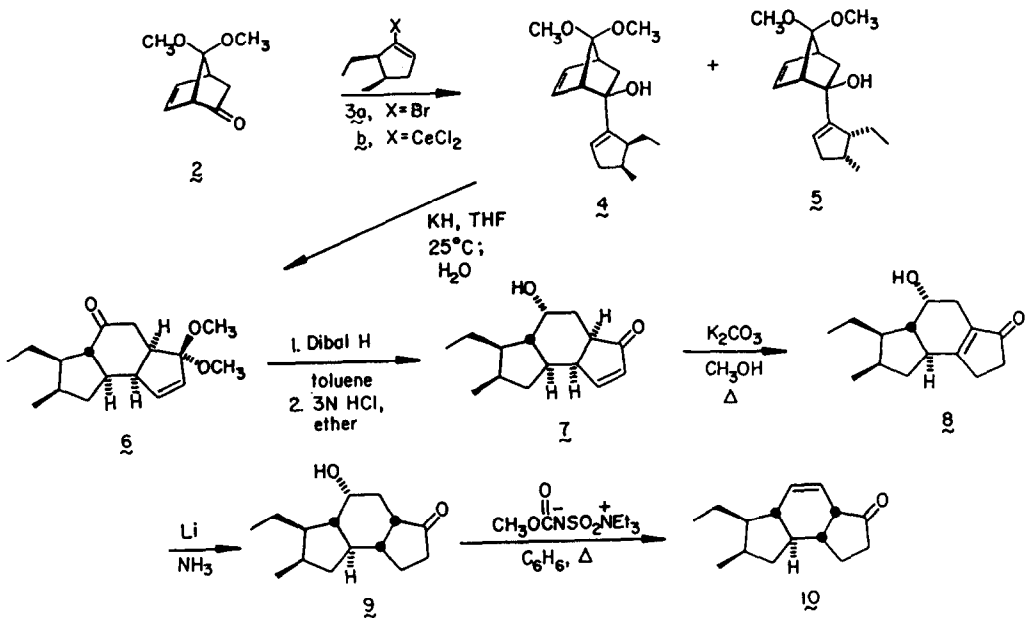
The coupling reaction of **2** with the known bromide **3a**[6] was effected in tetrahydrofuran solution via the dichlorocerium reagent **3b**[7] under the predescribed conditions.[1] Alcohols **4** and **5**, isolated in 83% yield following chromatographic separation, are distinguished by a strong diastereoselectivity bias (12:1, Scheme I). That the heavily predominant isomer is indeed **4** as anticipated was suggested by its ^{1}H NMR spectrum[1] and ultimately confirmed (as described below) by an X-ray analysis.

Exposure of **4** to an excess of potassium hydride in THF gave rise directly to the trans AB-locked tricyclic keto ketal **6** (72%).[8] This thermodynamic bias (see below)

Scheme I

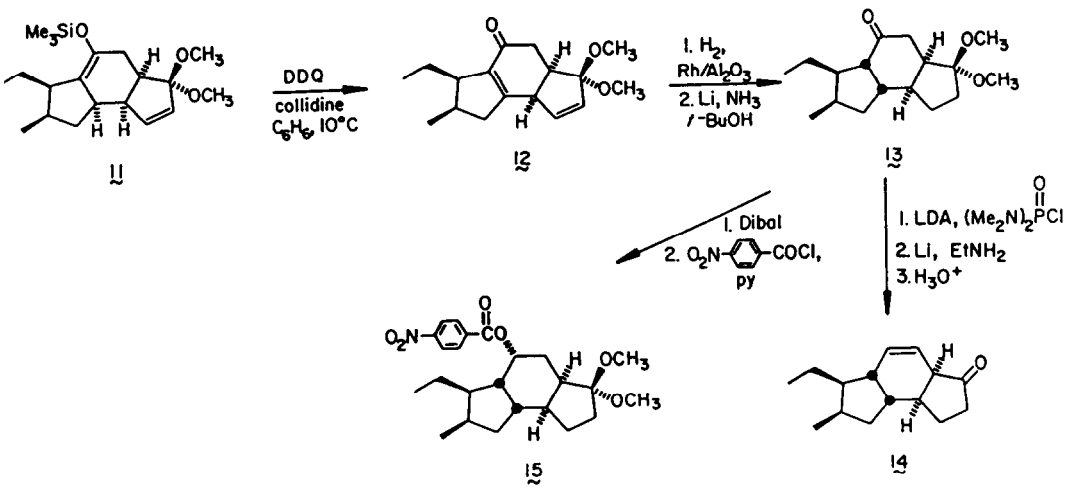


reflects control by the ethyl and methyl substituents.[9] Low-temperature Dibal-H reduction of **6** capitalizes on prior coordination to the β-OCH_3 of the dimethyl ketal to deliver exclusively the α (axial) alcohol. In contrast, L-Selectride reduction of **6** furnishes only the β (equatorial) alcohol. Subsequent acid hydrolysis led to one or the other stereochemically homogeneous cyclopentenone **7** (Scheme I) or **16** (Scheme III).

With ready access to **7**, the stage was now set for stereomodification of the B/C ring juncture and dehydration to introduce the double bond. Heating with K_2CO_3 in methanol induced essentially quantitative migration of the double bond to the internal site as in **8**. Dissolving metal reduction (83%) resulted in initial trans-locking of the A and C rings, in keeping with anticipated thermodynamic control of this protonation step. Additionally, subsequent kinetic α-protonation of the resulting enolate uniquely generated cis B/C stereochemistry. This last phenomenon is again readily understood in steric terms. Finally, dehydration of **9** by a cis-eliminative method[10] led to **10**.[11]

Several facets of the later stages of Scheme I have been found to be generally applicable and to hold potential for the stereocontrolled preparation of ikarugamycin analogs. For example, exposure of **4** to 1 equiv of n-BuLi in THF (23°C, 11 h) and *in situ* O-silylation of the regiospecifically generated enolate gave **11** (Scheme II).[12] Follow-

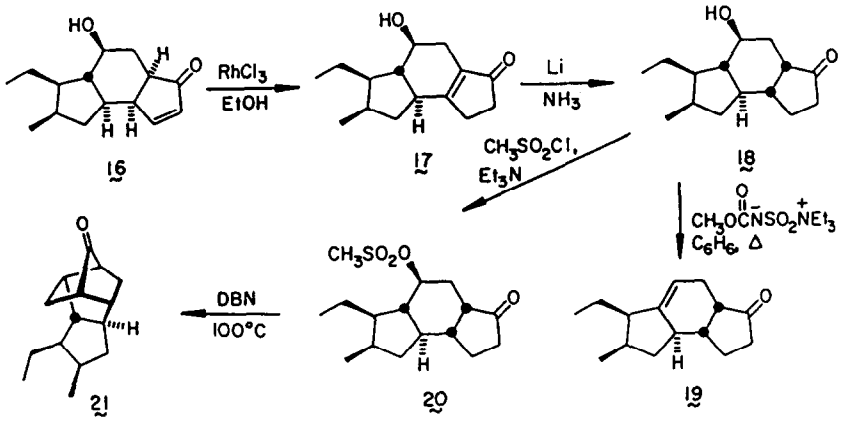
Scheme II



ing regiospecific oxidation to **12** and saturation of the lesser substituted double bond, dissolving metal reduction furnished **13** exclusively. The cis,anti arrangement of the newly introduced tertiary protons parallels our earlier observation. While the conversion of **13** to **14** illustrates an alternate method for the elaboration of the double bond, the transformation into p-nitrobenzoate **15** permitted crystallographic confirmation of all the preceding stereochemical assignments.[13]

As mentioned above, extension to the β-hydroxyl series is also feasible. However, at least two serious drawbacks have been uncovered during chemical investigation of these epimers. Compound **16** was converted (87%) to conjugated ketone **17** with rhodium trichloride in hot ethanol[14] and thence via lithium in liquid ammonia reduction to **18** (72%). As in the isomeric series earlier studied, anti/syn stereochemistry was again cleanly established. The remaining regiospecific dehydration of **18** could, however, not be satisfactorily effected. Under Burgess[10] or Mitsunobu conditions,[15] only **19** was formed, presumably as the combined result of the cis relationship to functional groups and the greater thermodynamic advantage offered by trisubstitution of the double bond. Activation of the hydroxyl center, for example by formation of **20**, and attempted E_2 elimination served only to produce **21** via 1,5-displacement within the enolate anion. Although this finding serves convincingly to reaffirm our stereochemical assignments, it does not advance the synthetic cause.

Scheme III



The convergent seven-step synthesis of **10** described herein is in principle adaptable to the optically active natural form, since resolution of **2** should be possible. Currently in progress are studies aimed at appending to **10** and to **14** the macrocyclic tetramic acid-containing ring.

Acknowledgment. This research was made possible by financial support provided by the National Institutes of Health (Grant GM-28468).

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(8) Routinely, **4** and **5** were not initially purified but rearranged as the 12:1 mixture. Direct recrystallization of the oxy-Cope reaction mixture from pentane afforded pure **6** in the stated yield.

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(11) All new compounds described herein gave correct elemental analysis and/or accurate mass spectral data. All ^{1}H NMR, ^{13}C NMR, and IR spectra are also in accord with the assigned structures.

(12) Controlled protonation of the lithium enolate gave the cis,syn,cis ketone which independently undergoes base-catalyzed isomerization (K_2CO_3, CH_3OH) to give **6**.

(13) We thank Dr. Y.-L. Hsu for this structure determination.

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