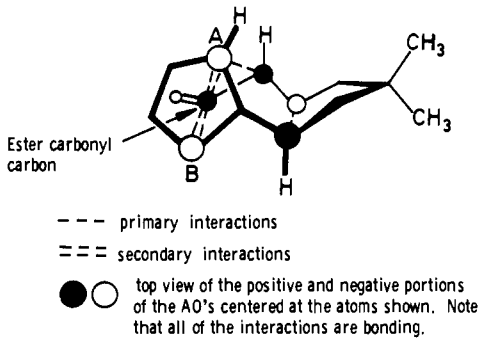
Scheme III



lecular approach is superior for the following reasons. (1) Excess diylophile is required in the intermolecular route to avoid side reactions. While it is generally easy to recover the diylophile, distillation and/or chromatography is required; with the intramolecular approach, the diylophile is built in, thereby obviating removal of excess diylophile. (2) The intermolecular trap leads to a mixture of stereoisomers whereas the intramolecular trap is highly stereoselective. (3) The intermolecular trap affords a mixture of regioisomers whereas the intramolecular trap is regiospecific. For example, an examination of diyl **1** reveals that the groups X, G, and the A-ring π bond can assume only one regioisomeric relationship upon closure to a tricyclopentanoid. This result is of use in regard to the synthesis of the coriolins and the antitumor agent diketocoriolin B.

We believe that the intramolecular 1,3-diyl trapping reaction represents a general and useful route to linearly fused tricyclopentanoids. We are presently exploring the conversion of **9** into (±)-hirsutene as well as the use of the intramolecular 1,3-diyl trapping reaction for the synthesis of the coriolins.

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(7) The selection of di(2,2,2-trichloroethyl) azodicarboxylate rather than dimethyl or diethyl azodicarboxylate for the Diels–Alder reaction allowed selective operation on the carbamate esters without concern for possible side reactions involving the α,β-unsaturated ester group.
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(9) Azo compound **8**: ^{1}H NMR ($CDCl_3$–Me_4Si) δ 7.01 (dt, 1 H, J = 8, 16 Hz, β-vinyl), 5.87 (dt, 1 H, J = 1, 16 Hz, α-vinyl), 5.40 and 5.17 (two br s, 1 H each, bridgeheads), 5.20 (t, 1 H, J = 8 Hz, C_7=C*H*R), 3.78 (s, 3 H, CO_2CH_3), 2.05 (dd, 2 H, J = 1, 8 Hz, CH_2CH=$CHCO_2CH_3$), 1.90 (d, 2 H, J = 8 Hz, $CH_2C(CH_3)_2$), 1.2 (m, 4 H, RCH_2CH_2R), 0.92 (s, 6 H, $(CH_3)_2C$).
(10) There is a minor, but as yet uncharacterized product which is formed.
(11) Linearly fused tricyclopentanoid **9**: IR (film) 3050, 2950, 1735, 1385, 1370, and 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$–Me_4Si) δ 5.2 (overlapping dt, 1 H, J = 2, 3 Hz, vinyl), 3.61 (s, 3 H, CO_2CH_3), 2.58 (d, 1 H, J = 8 Hz, $CHCO_2CH_3$), 1.03 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, note structure **9** for the numbering system used) 26.7, 25.9 and 28.2 (*gem*-CH_3 groups), 37.0, 39.9, 40.9 (C_{11}), 47.3, 47.6, 50.5, 50.7, 51.4 (CO_2CH_3), 51.6, 117.5 (C_4), 154.5 (C_3), 175.1 (CO_2CH_3).
(12) The secondary orbital interaction argument presumes that the degenerate pair of diyl NBMO's are perturbed so that the symmetric combination is the HOMO and the antisymmetric combination is the LUMO. For an analogous ordering of MO's see Siemionko, R.; Shaw, A.; O'Connell, G.; Little, R. D.; Carpenter, B. K.; Shen, L.; Berson, J. A. *Tetrahedron Lett.* **1978**, 3529–3532.
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(14) The reported yields are not optimized.

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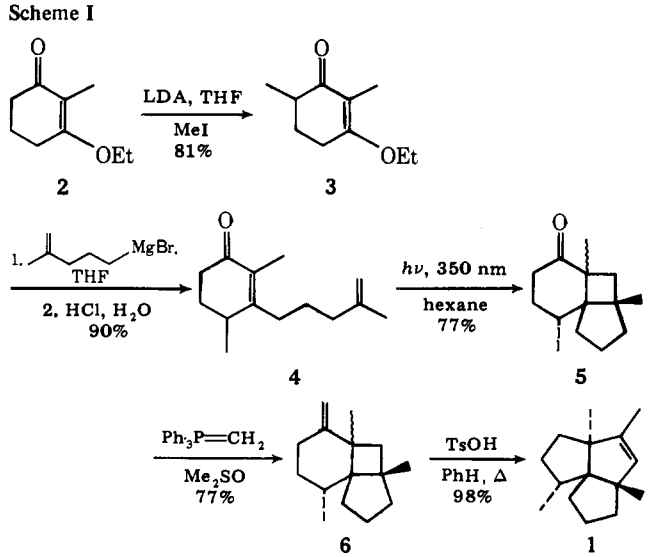
Total Synthesis of (±)-Isocomene

Sir:

The tricyclic sesquiterpene isocomene (**1**) was isolated in 1977 by Zalkow and co-workers[1] from rayless goldenrod (*Isocoma wrightii*), a plant notorious for its toxicity to cattle and sheep. Although compound **1** did not turn out to be the toxic constituent of the plant, its novel structure embodies an almost unique structural feature—three contiguous quaternary chiral centers—and constitutes a significant challenge to synthesis. In this communication we report the total synthesis of isocomene by an efficient route involving an intramolecular [2 + 2] photocycloaddition as the key bond-forming reaction (Scheme I). Though [2 + 2] cycloadditions are well known in synthesis, only recently has the intramolecular version been applied to a natural product.[2]

Enol ether **2**, readily available from dihydroresorcinol,[3] is methylated by the procedure of Stork and Danheiser[4] to obtain **3** (81%). This material reacts with the Grignard reagent prepared from 5-bromo-2-methyl-1-pentene[5] to afford an unstable alcohol which is treated with 5% aqueous HCl at 25 °C for 2 h to obtain dienone **4** (UV (hexane) λ_{max} 240 nm (log ϵ 4.14), 324 (1.52)) in 90% yield after simple chromatographic purification and bulb-to-bulb distillation. Irradiation of dienone **4** as a 10^{-2} M hexane solution with a Rayonet reactor using 350-nm lamps results in the formation of cycloadduct **5** (^{1}H NMR ($CDCl_3$) 0.83 (3 H, d, J = 7 Hz), 1.00 (3 H, s), 1.10 (3 H, s); IR (neat) 1705 cm^{-1}; UV (hexane) λ_{max} 283 nm (log

Scheme I



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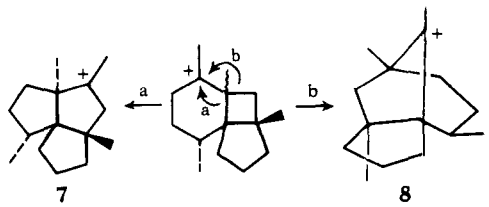
Scheme II



7 8

ϵ 1.50), tailing to 340 nm) as a waxy solid (mp 63–68 °C) in 77% yield. Detailed examination of the reaction product by ^{1}H NMR, ^{13}C NMR, LC, and GLC revealed the presence of only a single stereoisomer.

Although we were unable to induce **5** to undergo addition with a number of methylation reagents (MeLi, MeMgBr, $LiAlMe_4$) under a variety of conditions, seemingly owing to enolization,[6] it did react with methylenetriphenylphosphorane (2 equiv, Me_2SO, 70 °C, 3 days) to furnish hydrocarbon **6** (IR (neat) 1640 cm^{-1}). Upon treatment with *p*-toluenesulfonic acid (0.3 equiv, benzene, reflux, 1 h), **6** provided racemic isocomene in 98% yield (mp 60–62 °C), possessing spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) identical with those contained in comparison spectra graciously supplied by Professor Zalkow.

While 1,2-alkyl shifts in cyclobutyl carbinyl cations have been studied,[7] there are examples in which both modes of rearrangement to relieve the cyclobutane strain are observed. These are illustrated in Scheme II with our substrate. Migration of the ring fusion bond in sense a, as observed in this work, provides **7** and thence isocomene, while migration in sense b results in **8**. Examination of molecular models suggests that migration in sense a, at least for a cis-fused bicyclo[4.2.0] system, would be disfavored, since the migrating bond lies in the nodal plane of the p orbital. An intriguing explanation for the observed behavior would be the obtention of trans-fused[8] product from the cycloaddition, in which the ring fusion bond is favorably disposed for migration.

In conclusion, the synthetic approach described here stereoselectively provides (±)-isocomene in seven steps from an abundant, inexpensive, starting material. It is noteworthy for its brevity, high yield (>40%), and, *with the photoaddition step, production of three contiguous, quaternary chiral centers exclusively with the stereochemistry necessary for the natural product.* Its efficiency is illustrated by the preparation of ~3 g of the natural product by this route. We are continuing in our investigations of rearrangements of cyclobutylcarbinyl cations, including the acid-catalyzed reaction[9] of **5**.

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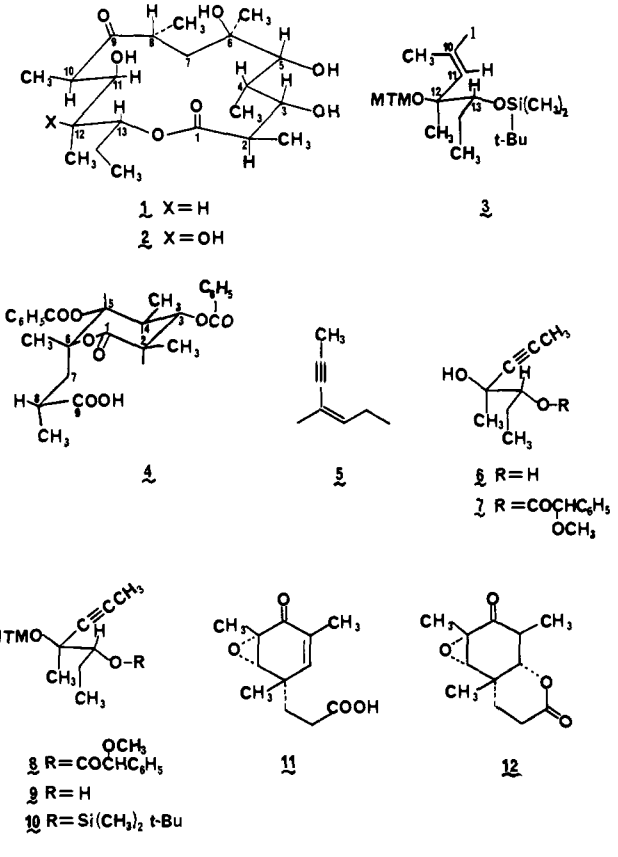
Total Synthesis of Erythromycins. 5. Total Synthesis of Erythronolide A

Sir:

The total synthesis of erythronolide B (**1**), the biosynthetic progenitor of all of the erythromycins, has previously been reported.[1,2] Herein we describe the first total synthesis of erythronolide A (**2**), the aglycone corresponding to the medically important antibiotic erythromycin A. The general strategy used for the synthesis of **2** is similar to that which led earlier to synthetic **1**, although there are major differences between the two syntheses with regard to segments of the synthetic plan and individual chemical steps. The construction of the erythronolide A molecule (**2**) involved the key optically active intermediates **3** (dextrorotatory form) and **4** (dextrorotatory form).

The synthesis of (+)-**3** in optically pure condition was accomplished as follows. Dehydration of 4-methyl-2-heptyn-4-ol (from reaction of 1-lithio-1-propyne and 2-pentanone in tetrahydrofuran (THF)) was effected by heating for 1 h at 100 °C with 0.1 equiv of *p*-toluenesulfonic acid monohydrate to afford after distillation a 93% yield of (*Z*)-4-methyl-4-hepten-2-yne (**5**) of 80% purity (^{1}H NMR and gas chromatographic analysis) along with the *E* isomer (10%) and 4-propyl-4-penten-2-yne (10%), bp 46 °C at 45 Torr.[3] Separation



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