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SYNTHETIC STUDIES ON ARENE-OLEFIN CYCLOADDITIONS. 11. TOTAL SYNTHESIS OF (-)-RETIGERANIC ACID

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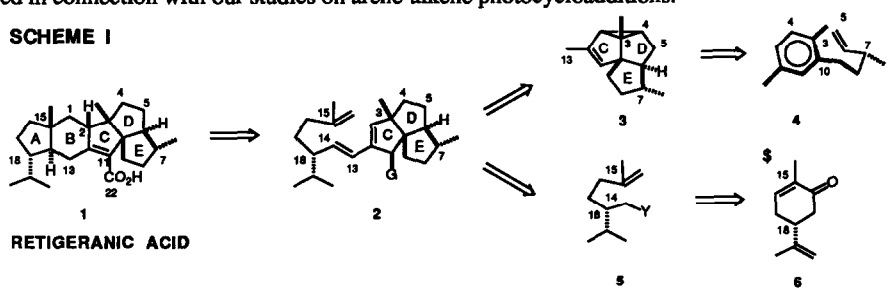
Abstract: *A convergent synthesis of (-)-retigeranic acid is described which is based on a Diels-Alder and arene-alkene cycloaddition strategy.*

Retigeranic acid A (**1**) is a constituent of Himalayan lichen which was shown by Shibata's group[1] to be a structurally unique member of the rare class of sesterterpene natural products.[2] The synthetic problems presented by this pentacycle, including associated *trans*-hydrindane and triquinane subunits punctuated by eight stereocenters, have been imaginatively addressed in contrasting syntheses reported by the groups of Corey, Hudlicky, and Paquette.[3] We report herein a convergent, enantiocontrolled route to (-)-retigeranic acid, developed in connection with our studies on arene-alkene photocycloadditions.[4,5]

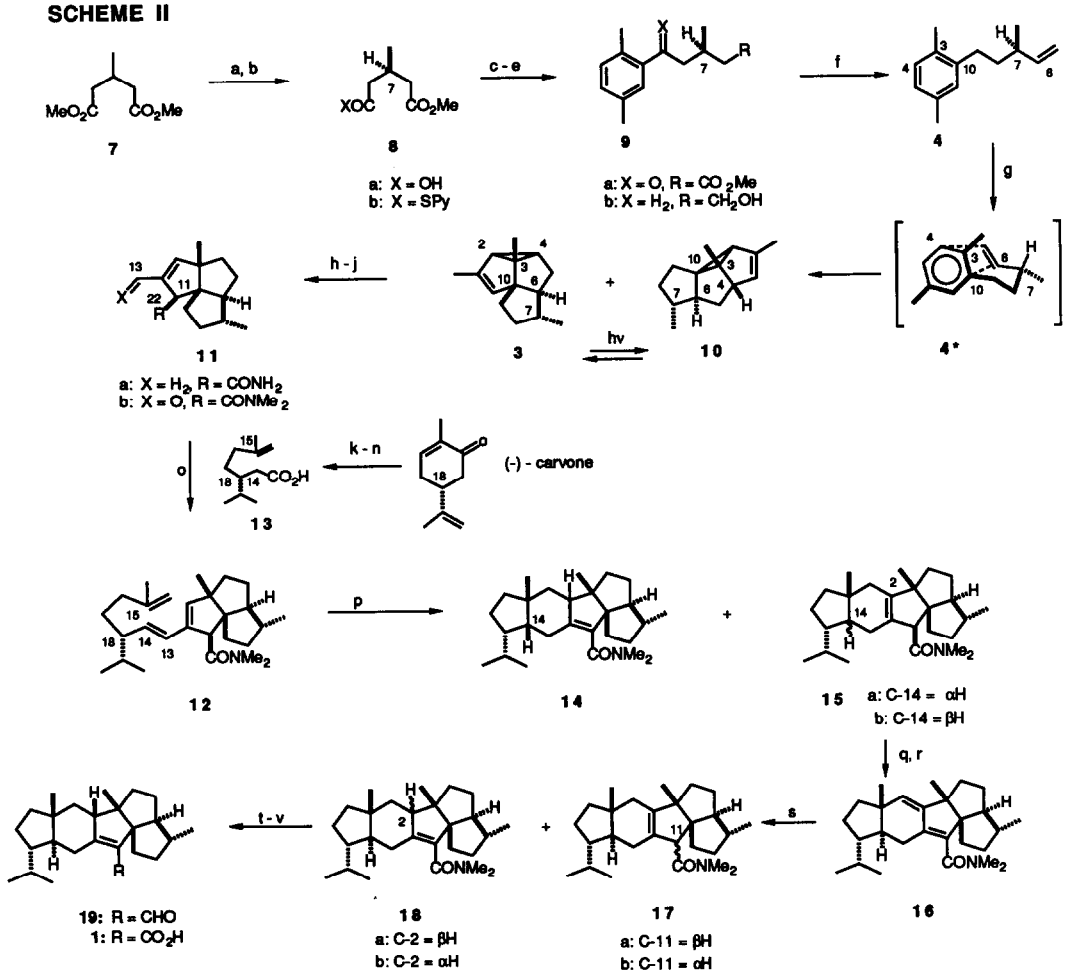
SCHEME I



Our approach to retigeranic acid was designed with the view that its *trans*-hydrindane and triquinane subunits could be assembled through the use of an intramolecular Diels-Alder reaction[6] and an arene-alkene cycloaddition,[5] respectively. As indicated in our starting plan (Scheme I), the great increase in structural complexity attending these two processes serves to minimize the number of steps needed to connect simple starting materials with the complex target. Thus, the Diels-Alder reaction would be expected to produce the highly complex pentacyclic target **1** from the less complex triquinane **2**, while the arene-alkene cycloaddition would provide the tricyclic core of the latter from the relatively simple arene **4**.

Since this plan calls for enantiomerically pure intermediates at the point of synthetic convergence, the first subgoal of our studies was the preparation of enantiomerically pure arene-alkene **4** (Scheme II). For this purpose, commercially available 3-methyl-glutaric acid was esterified and then converted through the use of pig liver esterase[7] to its half ester **8a**, which was then purified (>99%e.e.) by fractional recrystallization of its cinchonidine salt.[8] The homogeneous half ester (**8a**) was then converted to the S-pyridyl thioester[9] **8b** (96%)

SCHEME II



(a) pig liver esterase (ref. 7); (b) dipyridyl disulfide, Ph_3P, CH_2Cl_2, 36 h;.(c) p-xylyl bromide, Li^0, Et_2O; CuI, -78° to 0°C; addn. of **9a**, -78°, .5 h; (d) LAH, Et_2O; (e) 10% Pd-C, H_2 (1 atm), EtOH/$HClO_4$ (100:1), 15 h; (f) n-Bu_3P, o-nitro Ph-SeCN; 30% H_2O_2; (g) hv, vycor filter, C_6H_{12}, 7 h; (h) $HCONH_2$, CH_3COCH_3, t-BuOH, hv, Pyrex filter, 7 h; (i) KOH, DMSO; MeI 48 h; (j) SeO_2, t-BuOOH, CH_2ClCH_2Cl, reflux, 23 h; (k) $(Ph_3P)_3$ RhCl, H_2, PhH; (l) Br_2, HOAc; (m) 2.2% KOH; (n) $Ph_3P^+CH_3Br^-$, n-BuLi, THF; (o) **13**, LDA, THF, 50 °C, .5 h, then 0°C; add to **11b** at -78°C; warm to 25 °C; HOAc, dimethyl formamide dimethyl acetal, reflux, 2 h; (p) 250°C, $PhCH_3$, 22 h (q) mCPBA, NaOAc, CH_2Cl_2, 24 h; (r) t-BuOK, DMSO, 100°C; 5% HCl; (s) 10% Pd-C, PhH, H_2 (400 psi), 14 days; (t) LAH, THF, -5 °C (2 h), 25 °C (12 h); (u) PDC, CH_2Cl_2, 4 h; (v) ref. 2a

which reacted with the cuprate derived from commercially available bromo-*p*-xylene to give ketoester **9a** (90%). Reduction of the latter followed by hydrogenolysis of the resultant benzylic alcohol provided alcohol **9b** (93% for 2 steps). Dehydration of this alcohol according to the procedure of Grieco[10] furnished the desired photocycloaddition precursor **4** (84%) as a single enantiomer.

Construction of the triquinane subunit of **1** was then achieved by photolysis of arene-alkene **4** which provided a 1:2 mixture of cycloadducts **3** and **10** (72% combined yield). That these cycloadducts are related as

interconvertible vinylcyclopropane isomers was established by their photoequilibration starting with either **3** or **10**. The periselectivity and regioselectivity of the cycloaddition is consistent with expectations based on FMO theory[5k] or charge transfer arguments.[5m,n] The *exo*-orientation of the alkene and of the larger C-7 substituent (Me vs. H) in this cycloaddition are both in accord with the involvement of the exciplex or product determining transition state species **4*** in which steric, torsional, and bond angle strain are minimized. For preparative purposes, this sequence offers easy access to multi-gram quantities of cycloadduct **3**.

The next synthetic subgoal, conversion of cycloadduct **3** to **11a**, required attachment of C-22 to C-11. Previous studies from these laboratories[11] suggested that this objective could be achieved by the addition of a carbon free radical to the vinylcyclopropane. In accord with these earlier observations, addition of photogenerated formamide radical[12] to **3** gave triquinane **11a**, presumably by convex face addition to the alkene followed by cleavage of the cyclopropane bond which is better aligned (C-2,C-4> C-2,C-3) with the initially produced C-12 radical. Dimethylation of the addition product **11a** (80% yield at 67% conversion) and allylic oxidation[13] (53%) gave aldehyde **11b**.

Acid **13**, required for the construction of the Diels-Alder precursor **12**, proved to be readily derived[14] from R-(-)-carvone through the indicated sequence. Condensation of the dianion[15] of this acid with aldehyde **11b** produced a mixture of hydroxy acids which upon decarboxylative dehydration [16] gave only one alkene isomer (**12**: 65% overall yield). The thermal fate of the resultant triene **12** in the Diels-Alder step was now ready for evaluation. The general observation that simple 1,3,8-nonatrienes preferentially undergo *exo*-cycloadditions[17] suggested that a *trans*-fused hydrindane would be obtained. It was further expected that this exo-cycloaddition would occur on the convex (*beta*) face of the diene subunit, affording predominantly the desired C-14 isomer. In accord with these observations and expectations, thermolysis of triene **12** produced pentacycles **14**, **15a**, and **15b** (64%: 1:8.6:3, respectively) derived from cycloaddition and double bond migration. While post-cycloaddition double bond migration was expected to lead to C-2-*epi*-retigeranic acid, thereby requiring only epimerization of the C-2 center to reach the target, the observed alternative course of migration did not initially seem problematic, since conjugation of the double bond in **15a** with a carbonyl group and concurrent epimerization would also give **1**. However, all attempts to effect this isomerization failed. Consequently, an indirect approach was followed, entailing a two step conversion of **15a** to diene **16**. Hydrogenation of this diene produced in 95% yield a mixture consisting of the C-2 β-epimer **18a**, the α-epimer **18b**, and the C-11 epimers (**17a** and **17b**) in a ratio of 1:1.1:1.7. Efforts to improve the selectivity of this process were without success although it was possible to recycle the undesired isomers by conversion (95% yield) of **18b** to **17a,b** and the latter to **16** as given for the conversion of **15** to **16**. The identity of pentacycle **18a** was established by reduction to a mixture of the corresponding amine and alcohol and subsequent oxidation to the known aldehyde **19**. The synthesis was then completed by conversion of this aldehyde to retigeranic acid (**1**) and methyl retigeranate, both being identical by NMR, IR, MS, and chromatographic comparison with an authentic sample and material made by a different route.[18]

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