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Stereoselective, One-Step Assembly of the Strained Protoilludane Framework by Cobalt-Mediated Cyclization of an Acyclic Enediyne Precursor. A Total Synthesis of Illudol

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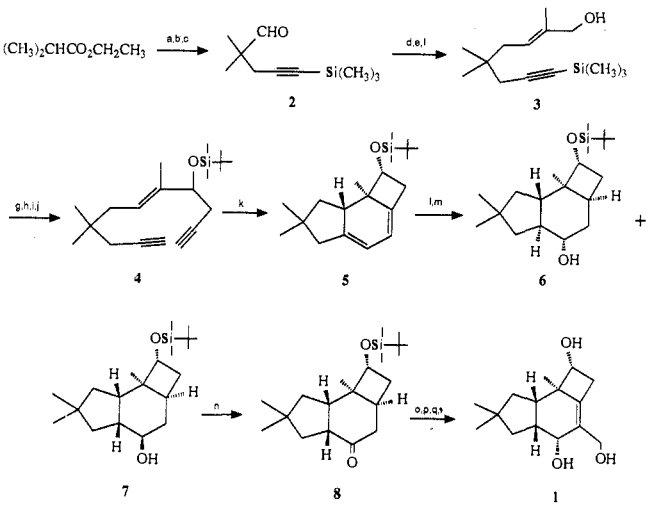
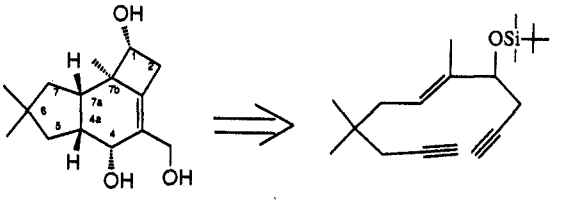
A number of basidiomycete sesquiterpenoids exhibit considerable toxic, antibiotic, and antitumor activity, including members of the protoilludane, illudane, marasmane, and sterpurane families.[1] The first type is considered to play an important biogenetic role with respect to the remainder.[1a,f,j,k,2] Among the synthetically most challenging protoilludanes ranks illudol (**1**), because it combines the task of constructing the unusual angular and strained hydrocyclobutaindane nucleus with that of controlling five contiguous stereocenters. Isolated by Anchel and co-workers some time ago,[1g,h,l,m] the molecule has seen only two total syntheses in the past two decades.[3,4] Like most other approaches to complex oligocycles, they relied on a stepwise strategy for ring formation.[5] Compared to these, a topologically more profound retrosynthetic disconnection envisions enediyne **4** as the direct precursor to the basic skeleton of **1**. Thus, it was hoped that stoichiometric $CpCo(CO)_2$ would convert **4** to CpCo-complexed **5** by intramolecular [2 + 2 + 2] cycloaddition,[6] the ligand **5** possessing the necessary functionality to allow its elaboration to **1** (Scheme I). This anticipation notwithstanding, there was considerable concern about the lack of precedence for such a transformation, featuring internal double bonds flanked by two alkynes, all previous examples leading to unstrained systems and suffering much lesser encumbrance by substituents.[6] Moreover, related terminal enediyne cyclizations were shown to be complicated by isomerizations involving hydrogen shifts.[7] We now report the realization of Scheme I, incorporating the stereoselective assembly of **5** and its conversion to racemic illudol (**1**).[8]

Scheme I[a]



[a] (a) (i) $[(CH_3)_2CH]_2NLi$ (1.0 equiv), THF, −78 °C, 2 h; (ii) 3-bromo-1-(trimethylsilyl)propyne (1.0 equiv), −78 to 23 °C, 12 h, 94%; (b) $LiAlH_4$ (0.5 equiv), $(CH_3CH_2)_2O$, 23 °C, 4 h, 100%; (c) (i) $(COCl)_2$, DMSO, −78 °C, 1.5 h; (ii) $(CH_3CH_2)_3N$, −78 to 23 °C, 4 h, 97%; (d) (i) $CH_3S(O)CH_2Li$ (1.4 equiv), $(C_6H_5)_3P^+CH_2OCH_3Cl^-$ (1.5 equiv), THF, 0 °C for 5 h, 23 °C for 1 h; (ii) **2** (1.0 equiv), 0–23 °C, 4.5 h; (iii) 1 N HCl, 23 °C, 18 h, 86%; (e) $(C_6H_5)_3P{=}C(CH_3)CO_2CH_2CH_3$ (1.2 equiv), CH_2Cl_2, 23 °C, 48 h, 92%; (f) $[(CH_3)_2CHCH_2]_2AlH$ (2.05 equiv), CH_2Cl_2, −78 °C, 2 h, 99%; (g) (i) $(COCl)_2$, DMSO, −78 °C, 1.5 h; (ii) $(CH_3CH_2)_3N$, −78 to 23 °C, 3.5 h, 98%; (h) propynylmagnesium bromide (2.5 equiv), $(CH_3CH_2)_2O$, 0 °C, 15 min, 89%; (i) K_2CO_3 (1.2 equiv), CH_3OH, 23 °C, 24 h, 100%; (j) $[(CH_3)_3C](CH_3)_2SiCl$ (1.8 equiv), imidazole, DMF, 23 °C, 36 h, 99%; (k) (i) $CpCo(CO)_2$ (1.1 equiv), toluene, 110 °C, *hν*, 6 h; (ii) $CuCl_2 \cdot 2H_2O$ (2.5 equiv), 1,2-dimethoxyethane, 23 °C, 3 h, 92%; (l) (i) Li (excess), NH_3–$(CH_3)_3COH$–THF (8:2:3), 33 °C, 5 min; (ii) NH_4Cl (20 equiv), −33 °C, 62%; (m) (i) B_2H_6 (3.0 equiv), THF, 23 °C, 3 h; (ii) H_2O_2 (5.0 equiv), K_2CO_3 (1.2 equiv), 65 °C, 1.5 h, 77% (**6**:**7**, 2:3); (n) (i) $(COCl)_2$, DMSO, −78 °C, 2 h; (ii) $(CH_3CH_2)_3N$, −78 to 23 °C, 3 h; (iii) K_2CO_3 (1.5 equiv), CH_3OH, 23 °C, 4.5 h, 79%; (o) (i) $[(CH_3)_2CH]_2NLi$ (2.0 equiv), THF, 23 °C, 3.5 h; (ii) CO_2 (excess), −78 °C, 5 min; (iii) 1 N HCl (2.0 equiv), −78 to 0 °C; (iv) CH_2N_2 (10 equiv), $(CH_3CH_2)_2O$, 0–23 °C, 2 h, 56%; (p) (i) NaH (1.2 equiv), THF, 0 °C, 2.5 h; (ii) C_6H_5SeCl (0.95 equiv), −78 °C, 0.5 h; (iii) H_2O_2 (excess), NH_4Cl (20 equiv), CH_2Cl_2, 0 °C, 1.5 h, 40%; (q) $NaH_2Al(OCH_2CH_2OCH_3)_2$ (5.0 equiv), C_6H_6, 23 °C, 24 h, 54% (17:37 β:α); (r) $(CH_3CH_2CH_2CH_2)_4N^+F^-$ (1.0 equiv), THF, 23 °C, 12 h, 74%.



Alkylation of the enolate of ethyl 2-methylpropanoate with 3-bromo-1-(trimethylsilyl)propyne, followed by reduction of the ester function to the corresponding alcohol and subsequent oxi-

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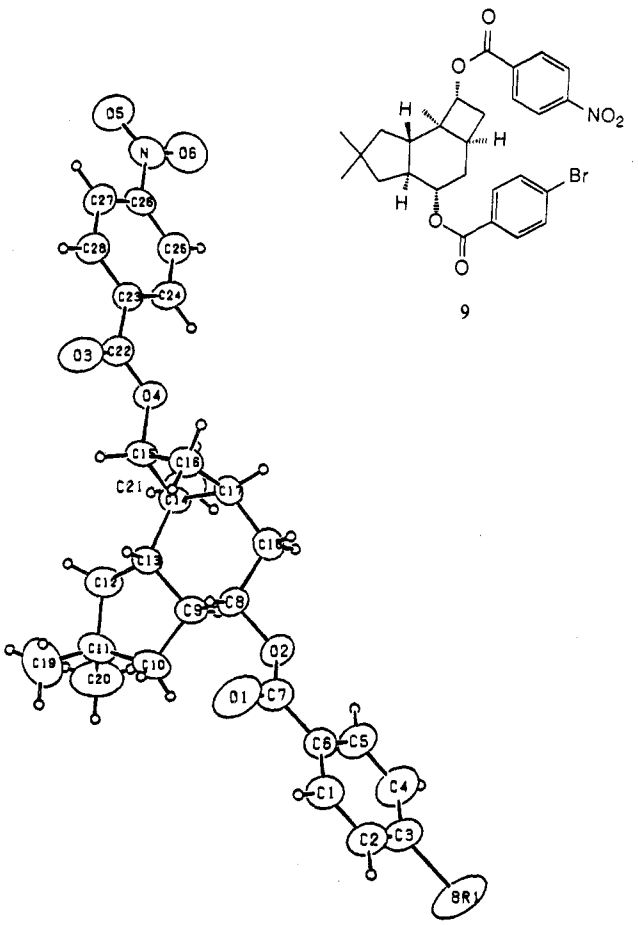

9

Figure 1. ORTEP representation and Chemtext diagram of 9.

dation, gave aldehyde **2**. One-carbon homologation through sequential Wittig reaction and hydrolysis of the enol ether product mixture furnished an aldehyde that was converted by [(ethoxycarbonyl)ethylidene]triphenylphosphorane to the corresponding α,β-unsaturated ester (>95% *E*). Its reduction provided alcohol **3**, which was elaborated by standard methods to the cyclization substrate **4**. Gratifyingly, this enediyne was rearranged by $CpCo(CO)_2$ directly to the highly air sensitive diene **5** as the only diastereomer (^{1}H NMR analysis). Although not demonstrated here rigorously, it is clear from model studies[7] that this cyclization is catalytic. Remarkable are the efficiency (92%!) and stereoselectivity (complete) of this process. The relative configurations of C-1, -7a, and -7b could not be deduced from spectroscopic data, although that of the latter two was assumed to be as shown, retaining the stereochemistry of the alkene unit.[6] Since Matsumoto had demonstrated that the C-1 stereocenter could be controlled, if necessary, at a later stage,[3] diene **5** was elaborated further.

Dissolving lithium in NH_3(liq) reduced the C-2a,3 π-bond to furnish the *cis*-bicyclo[4.2.0]octane stereochemistry,[9] the remaining unsaturation being removed by regio- but (surprisingly) not stereospecific hydroboration–oxidation, generating **6** and **7** in a ratio of 2:3. The structure of **6** (and thus the stereochemical outcome of the cyclization of **4**) was confirmed through an X-ray structural analysis of its derivative **9** (Figure 1),[10] the result of 4-bromobenzoylation, desilylation, and finally, 4-nitrobenzoylation at C-1.

Oxidation of the mixture of **6** and **7** allowed the chromatographic separation of the corresponding ketones. The subsequent base-catalyzed isomerization of the undesired isomer (equilibrium ratio 5:1) led to **8** (20% from ethyl 2-methylpropanoate), a molecule very similar to an intermediate in Semmelhack's strategy to **1**,[4] that protocol guiding the completion of the present approach. Thus, carboxylation of the enolate of **8** with CO_2, esterification with CH_2N_2, and selenium-mediated oxidation (a sequence that was not optimized in its efficiency, the relatively low yield constituting the result of incomplete conversions) generate the oxo ester precursor to **1**, whose reduction with sodium bis(methoxyethoxy)aluminum hydride gave rise to a mixture of C-4 isomeric diols, that containing the desired 4α-OH configuration predominating (37:17). Finally, deprotection of the C-1 hydroxy group supplied illudol (**1**), spectroscopically identical with the naturally occurring material.[11]

The assembly of **1** is the first in which all three rings are constructed in a step that features CpCo as a mediator in the completely stereospecific generation of a strained tricycle. The selective elaboration of the diene unit in **5**, a functional moiety that is the product of many related cyclizations, points to other applications of this strategy to the synthesis of complex molecules.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond angles, and bond distances for **9** and ^{1}H NMR, ^{13}C NMR, IR, HRMS, and combustion analysis data for **1–9** and intermediates (16 pages). Ordering information is given on any current masthead page.

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(10) Executed by Dr. F. J. Hollander, Chexray facility, University of California at Berkeley: triclinic; space group $P\bar{1}$, a = 8.8169 (10) Å, b = 11.6852 (19) Å, c = 14.3025 (19) Å, α = 69.878 (10)°, β = 78.541 (10)°, γ = 85.512 (11)°, V = 1356.0 (4) Å^3, Z = 2, μ_{calcd} = 15.4 cm^{-1}, ρ_{calcd} = 1.36 g cm^{-3}; Enraf-Nonius CAD4; Mo Kα radiation [λ(Kα) = 0.710 73 Å]; 3° ≤ 2θ ≤ 45°; 3546 unique reflections, of which 2352 were treated as observed [$F^2 \geq 3\sigma(F^2)$]; an absorption correction was not applied; R = 0.0403, R_w = 0.0536.

(11) We thank Professors T. C. McMorris and M. F. Semmelhack for providing us with a sample of natural illudol and spectral data of synthetic illudol, respectively.

Complexation Control of Pericyclic Reactions: Supramolecular Effects on the Intramolecular Diels–Alder Reaction†

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The development of artificial enzyme-like catalysts is being pursued from two directions, the immunological[1] and the synthetic.[2] Critical to the success of these catalysts is their ability to selectively bind and stabilize the transition state of the reaction.[3] Pericyclic processes are attractive targets for catalyst design due to their widespread use in synthesis, their uncomplicated mechanisms, and the possibility of using specific binding interactions to overcome the entropic demands of their ordered transition states.[4] In this paper we demonstrate that synthetic receptors with carefully positioned binding groups can modulate the rate of a cycloaddition reaction by selectively binding to different structures on the reaction pathway.

Our target reaction was the intramolecular Diels–Alder (IMDA) reaction of disubstituted *N*-furfurylfumaramide derivatives[5] **1** (Scheme I). This process is characterized by substantial

† Presented in part at the 200th National ACS meeting, Washington, DC, August 1990.

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