Biomimetic Diastereoselective Total Synthesis of *epi*-Illudol *via* a Transannular Radical Cyclizations Strategy

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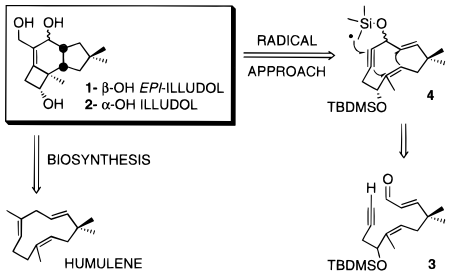
Protoilludanes, with a unique tricyclic carbon skeleton, belong to a series of sesquiterpene metabolites produced by fungal basidiomycetes.[1] These compounds, which generally show antibacterial activity, are formed biogenetically from farnesyl pyrophosphate[2] *via* the 11-membered ring humulene, by a macrocyclization−transannular carbocationic cyclizations process.

Among these protoilludanes, *epi*-illudol (**1**) and illudol (**2**) pose a real synthetic challenge because of their unusual tricyclic structure containing a methylenecyclobutane moiety and their five contiguous stereogenic centers (Scheme 1). Illudol (**2**) was isolated in 1967 by Anchel,[1b] from the poisonous mushroom *Clitocybe illudens*, commonly named "Jack o'Lantern" because of its bioluminescent property. The C-4 epimer, *epi*-illudol (**1**), was extracted by Arnone[1a] in 1989, from *Clitocybe candicans*, a nontoxigenic fungus. Three total syntheses[3] of illudol (**2**) have already been published. The more efficient and elegant was based on a cobalt-catalyzed [2 + 2 + 2] cycloaddition[3c] and afforded the protoilludane framework in a one-step assembly from an acyclic precursor. *epi*-Illudol (**1**) was present in these three different non-stereoselective syntheses of racemic illudol as the minor diastereomer.

*Herein, we present the first diastereoselective total synthesis of epi-illudol (**1**).* A one-pot cascade of three radical cyclizations including two transannular processes from an 11-membered ring affords, directly and diastereoselectively, the linear 4,6,5-ring fused skeleton of *epi*-illudol.

Inspired by the biosynthetic sequence, we designed a biomimetic strategy to assemble the strained tricyclic skeleton of illudol from an 11-membered cycloalkadienynol *via* a cascade of radical transannular cyclizations[4] from its bromomethyldimethylsilyl (BMDMS) ether at the 4-position. This retrosynthetic sequence deserves several comments. The well-established highly regioselective and stereoselective 5-*exo-dig* radical

Scheme 1



cyclization of α-silyl radicals generated from BMDMS propargyl ethers[5] would afford, after Tamao oxidation, the 2-methylenepropane-1,3-diol moiety present in these natural frameworks. Preliminary results have shown the high chemoselectivity of this cyclization for mixed allylic and propargylic BMDMS ethers precursors toward the 5-*exo-dig* process *vs* the 5-*exo-trig* one. Gratifyingly this chemoselectivity is total when an 11-membered cyclic ether is involved.[6] We anticipated that the very high reactivity and the space arrangement of the vinyl radical, created by a 5-*exo-dig* cyclization of radical **4**, should allow the success of the first unfavorable[7] 4-(π-*exo*)-*exo-trig*/9-(π-*endo*)-*endo-trig* process of this cascade. Finally, a more favorable 6-*exo-trig*/5-*endo-trig* cyclization would achieve the preparation of the illudol framework.

We first had to find a straightforward entry to the requisite precursor **3**. We planned to prepare the highly strained cycloundecadienyne precursor using two alternative ways: (i) the nucleophilic 1,2-addition of an acetylide to an enal as reported by Wiemer[8] and (ii) the Nozaki−Kishi coupling[9] between an iodoalkyne and an aldehyde function as described by Fallis.[9d]

We describe, here, in detail the successful sequences followed to prepare the natural sesquiterpene (Scheme 2). In the presence of 1 mol % of palladium diacetate and 2.5 mol % of bis(diphenylphosphinoethane), 1,2-epoxy-2-methylbut-3-ene[10] (**6**) generates a π-allyl palladium complex. Lithium enolate **5**, prepared *in situ* from ethyl isobutyrate and LDA, reacted with the complex in THF at room temperature, to produce regio- and stereoselectively the allylic alcohol **7** in 90% yield, as a 80:20 (*E:Z*) mixture of stereomers. The successful use of this unusual (nonstabilized) nucleophilic species in a palladium-catalyzed opening of vinyl oxiranes[11] is surprising and quite useful in synthesis. In our case, it makes possible a fast and straightforward preparation of the needed macrocycle **11**, using the sequence depicted below. A TBDMS protection, followed by a LAH reduction of the ester group, afforded quantitatively, the monoprotected diol. The corresponding aldehyde, quanti-

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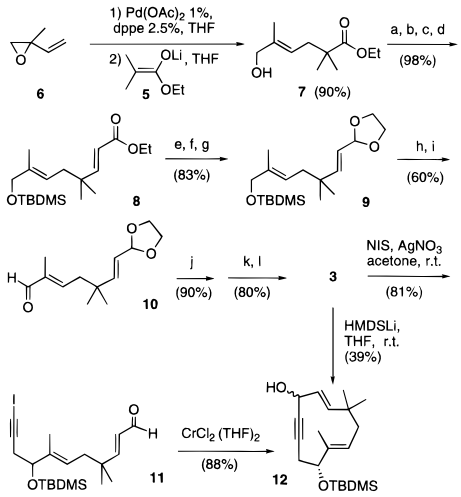
Scheme 2[a]



[a] (a) TBDMSCl, 4-DMAP, Et_3N, CH_2Cl_2, room temperature (rt); (b) LAH, Et_2O, 0 °C to rt; (c) Swern oxidation; (d) $(EtO)_2POCH_2COOEt$, LiCl, Et_3N, CH_3CN, rt; (e) DIBAL-H, CH_2Cl_2, −78 °C to rt; (f) Swern oxidation; (g) $(HOCH_2)_2$, $HO(Bu)_2SnOSn(Bu)_2NCS$, benzene reflux; (h) *n*-Bu_4NF, THF, rt; (i) DMSO, NEt_3, SO_3−pyridine complex, CH_2Cl_2, rt; (j) propargyl Grignard, Et_2O, −40 °C; (k) TBDMSCl, imidazole, DMF; (l) APTS, acetone, H_2O, Δ.

tatively prepared by Swern oxidation, was engaged in the Horner−Wadsworth−Emmons reaction under the mild conditions of Masamune and Roush[12] to give *E*-α,β-unsaturated ester **8** in 98% yield. Reduction of the latter with DIBAL-H, followed by Swern oxidation of the resulting allylic alcohol, gave the enal in 91% overall yield from **8**. Aldehyde acetalization using the Otera procedure[13] efficiently produced diene **9** (91%), and desilylation then furnished the allylic alcohol. This was converted by the SO_3−pyridine complex modification of the Moffatt oxidation[14] to *E*-enal **10** in 60% overall yield. Nucleophilic addition of propargylic Grignard to the aldehyde led to the homopropargyl alcohol in 90% yield, which was silylated in 80% yield using the imidazole−DMF conditions.[15] A final deprotection gave the expected undecadienynal **3**, which was submitted to mild iodination conditions[16] to form the iodoalkyne **11** in 81% overall yield. Upon dropwise treatment with base (LiHMDS generated *in situ*), acetylenic aldehyde **3** (0.8 M) in benzene at room temperature undergoes a clean but incomplete macrocyclization to provide the cycloundecadienyol **12** in 39% yield (recovered starting material 23%). A more successful approach was the slow addition in 6 h of the iodoalkyne **11** (1.2 mmol, 0.015 M) in THF, to a suspension of chromium chloride (0.16 M) in THF[9d] which produced **12** in 88% yield. In both cases, the product was isolated as an inseparable mixture of two diastereomers in a 3:1 ratio. Both were fully characterized by spectroscopic measurements, but at this stage of the synthesis, it was impossible to ascertain the relative configuration of the two stereogenic centers. BMDMS ether **13**, prepared in quantitative yield by silylation using 4-DMAP and Et_3N in dichloromethane (Scheme 3), was submitted to the usual tin-mediated radical generation (substrate 0.025 M Bu_3SnH, 2 × 10^{-4} mol h^{-1}, AIBN, benzene) followed by Tamao oxidation[17] (H_2O_2, $KHCO_3$, KF) to lead very cleanly and diastereoselectively to the tricyclic 4,6,5-framework of monosilylated *epi*-illudol **14** in 47% yield. Surprisingly, the Tamao oxidation

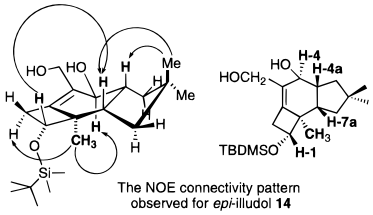
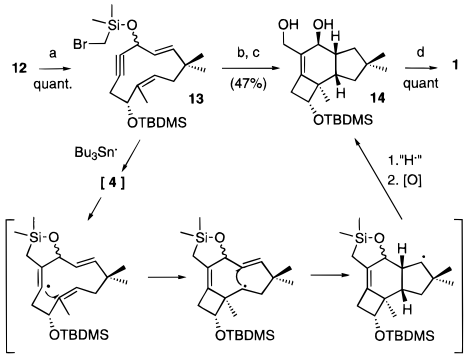


Figure 1.

Scheme 3[a]



[a] (a) BMDMSCl, 4-DMAP, NEt_3, CH_2Cl_2; (b) Bu_3SnH, AIBN, benzene Δ; (c) H_2O_2, $KHCO_3$, KF, THF−MeOH; (d) *n*-Bu_4NF, THF.

did not affect the TBDMS ether, and as a result, desilylation was needed to finally obtain *epi*-illudol (**1**), formed as one unique diastereomer. Full characterization[18] by IR, ^1H, ^{13}C, COSY, NOE NMR, and MS of the silylated *epi*-illudol **14** supports the proposed structure. Particularly, irradiation of the angular CH_3 at 0.95 ppm (^1H NMR, 500 MHz, $CDCl_3$) gave NOE enhancement at H-4, thus confirming the β-position of the OH-4 (Figure 1). The irradiation of the H-1 at 3.88 ppm produce enhancements for H-7a and H-4a, demonstrating the *syn* relationship between these hydrogen atoms. Finally, the synthetic *epi*-illudol (**1**) was spectroscopically (IR, ^1H, ^{13}C NMR) identical with the authentic sample from the Nasini group.[1a] Considering that, in the cascade process, the two already existing stereogenic centers are not directly affected, the formation of *epi*-illudol in 47% yield suggests that it originates from the major diastereomer of macrocycle **13**, which, therefore, bears H-1 and H-4 in an *anti* relationship. No trace of illudol derivatives was detected. This is probably the result of unfavorable interactions, between the 4α-hydroxy and the 7b-methyl, developed during the radical transannular closure.

In conclusion, the racemic sesquiterpene *epi*-illudol has been synthetized in 18 steps from isoprene oxide. The two key steps are the 11-membered macrocyclization and the cascade of transannular radical cyclizations, which allowed, in a one-pot process, the stereoselective construction of the intriguing tricyclic framework having five contiguous stereogenic centers. Moreover, this successful approach opens an unprecedented pathway for the syntheses of different natural active products of the protoilludene family, such as the tsugicolines A, B, and C[1h] or the armillyl orsellinate,[1e−g] a goal which is under active investigations in our group.

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Supporting Information Available: Summary of procedures and characterizations data for **7**, **8**, **9**, **10**, **3**, **11**, **12**, **13**, **14**, and **1** (9 pages). See any current masthead page for ordering and Internet access instructions.

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