ORGANIC LETTERS

2003
Vol. 5, No. 13
2295−2298

Enantiospecific First Total Synthesis and Assignment of Absolute Configuration of the Sesquiterpene (–)-Cucumin H†

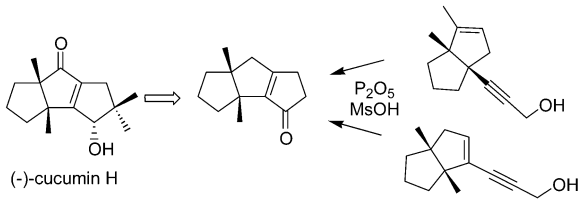
A. Srikrishna* and Dattatraya H. Dethe

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

ask@orgchem.iisc.ernet.in

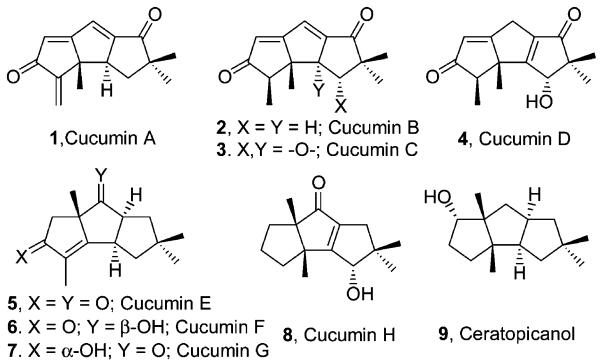
Received April 14, 2003

ABSTRACT



The first total synthesis of the sesquiterpene (–)-cucumin H, a linear triquinane isolated from *Macrocystidia cucumis*, has been accomplished starting from (*R*)-limonene employing two different cyclopentannulation methodologies, which in addition to confirming the structure also established the absolute configuration of the natural product.

Among the cyclopentanoid natural products, linearly fused triquinane sesquiterpenes have been encountered in increasing numbers from diverse natural sources. The presence of an interesting tricyclic carbon framework coupled with the functional group diversity, stereochemical intricacies, and promising biological activities have sustained a high level of synthetic interest in this family of natural products.[1] In 1998, research groups of Steglich and Anke reported[2] the isolation of eight new linear triquinane sesquiterpenes from mycelial cultures of the agaric *Macrocystidia cucumis*, four belonging to the hirsutane group (cucumins A−D, **1**−**4**), three to the cucumane group (cucumins E−G, **5**−**7**), and one to the ceratopicane group (cucumin H, **8**). Cucumin H (**8**) is the second member of the ceratopicane group to be isolated from Nature, whose first member ceratopicanol (**9**) was reported in 1988[3] by Hanssen and Abraham from the agar cultures of ascomycete *Ceratosystis piceae*. Cucumins



A−C were found to exhibit high cytotoxic and antimicrobial activities. The structure of cucumin H (**8**) was determined through incisive high-field NMR studies. However, due to

† Dedicated with respect and affection to Professor Goverdhan Mehta on his 60th birthday.

(1) Recent reviews: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647.

(2) Hellwig, V.; Dasenbrock, J.; Schumann, S.; Steglich, W.; Leonhardt, K.; Anke, T. *Eur. J. Org. Chem.* **1998**, 73.

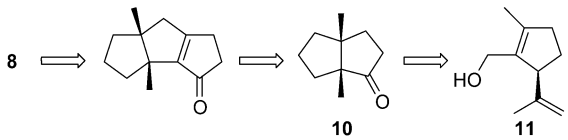
(3) Isolation of ceratopicanol: Hanssen, H.-P.; Abraham, W.-R. *Tetrahedron* **1988**, *44*, 2175. For synthesis, see: Mehta, G.; Karra, S. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1367. Clive, D. L. J.; Magnuson, S. R. *Tetrahedron Lett.* **1995**, *36*, 15. Baralotto, C.; Chanon, M.; Julliard, M. *J. Org. Chem.* **1996**, *61*, 3576. Paquette, L. A.; Geng, F. *J. Am. Chem. Soc.* **2002**, *124*, 9199. Anger, T.; Graalmann, O.; Schroder, H.; Gerke, R.; Kaiser, U.; Fitjer, L.; Noltemeyer, M. *Tetrahedron* **1998**, *54*, 10713. Mukai, C.; Kobayashi, M.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225.

10.1021/ol034635p CCC: $25.00
Published on Web 06/04/2003

the paucity of the material, assignment of the absolute configuration and evaluation of the biological profile were not addressed. Herein, we report the enantiospecific first total synthesis of (−)-cucumin H ((−)-**8**) along with three other regio- and stereoisomers, which not only confirmed the stereostructure but also established the absolute configuration of the sesquiterpene.

The presence of an interesting triquinane carbon framework comprised of six quaternary carbon atoms (three sp^3 and three sp^2) and a γ-hydroxyenone moiety coupled with its low natural abundance has made cucumin H (**8**) an important synthetic target. Retrosynthetically it was envisioned that the Nazarov cyclization based cyclopentannulation of bicyclic ketone **10** provides a convenient route for cucumin H (Scheme 1). For the enantiospecific synthesis of

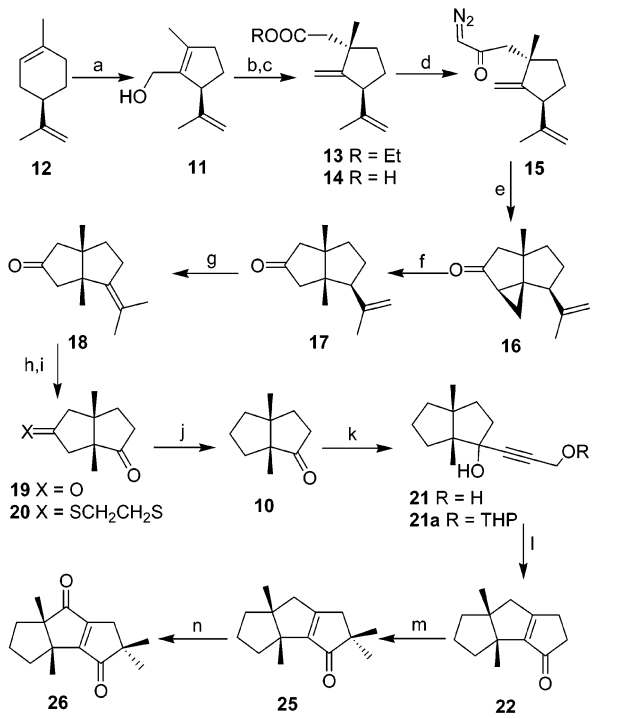
Scheme 1



bicyclic ketone **10** containing two vicinal ring junction quaternary carbon atoms, allyl alcohol **11**, derived from readily and abundantly available monoterpene (*R*)-limonene, was chosen as the chiral starting material visualizing the isopropenyl group as a masked ketone as well as a disposable chiral director.

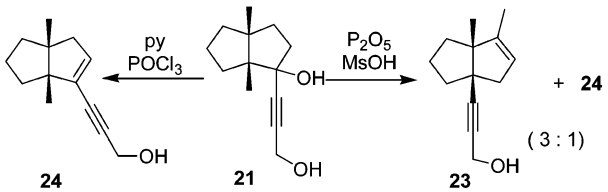
The synthetic sequence starting from (*R*)-limonene (**12**) is depicted in Scheme 2. To begin with, (*R*)-limonene (**12**) was converted into allyl alcohol **11** in three steps.[4] A Claisen rearrangement−intramolecular cyclopropanation−regiospecific cyclopropane ring cleavage sequence was contemplated for the simultaneous creation of the two quaternary carbon atoms and annulation of the second cyclopentane ring on cyclopentenylmethanol **11**. Thus, Johnson's ortho ester Claisen rearrangement[5] of allyl alcohol **11** with triethyl orthoacetate and propionic acid generated the γ,δ-unsaturated ester **13** in a highly stereoselective manner, which on hydrolysis furnished acid **14**. Anhydrous copper sulfate−copper catalyzed decomposition[6] of diazo ketone **15**, obtained from acid **14**, in refluxing cyclohexane resulted in the intramolecular cyclopropanation leading to stereo- and regiospecific formation of the tricyclic ketone **16**, $[\alpha]^{25}_D$ −115 (*c* 1.65, $CHCl_3$). Treatment of tricyclic ketone **16** with lithium in liquid ammonia, predictably,[7] furnished bicyclic ketone **17**, $[\alpha]^{27}_D$ +140 (*c* 3, $CHCl_3$), mp 41−43 °C, via selective cleavage of the C-2−C-3 bond. After successfully creating

Scheme 2[a]



[a] Reagents, conditions, and yields: (a) ref 4; (b) $MeC(OEt)_3$, $EtCO_2H$, sealed tube, 180 °C, 5 days, 80%; (c) 10% aq NaOH, MeOH, reflux, 8 h, 94%; (d) (i) $(COCl)_2$, C_6H_6, rt, 2 h; (ii) CH_2N_2, Et_2O, rt, 2 h; (e) Cu−$CuSO_4$, *c*-C_6H_{12}, *W*-lamp, reflux, 5 h, 70% (from the acid **14**); (f) Li, liquid NH_3, −33 °C, 15 min, 85%; (g) *p*TSA, CH_2Cl_2, rt, 2 days, 99%; (h) O_3/O_2, CH_2Cl_2−MeOH (5:1), −70 °C; Me_2S, rt, 5 h; 90%; (i) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, C_6H_6, 0 °C, 1 h, 80%; (j) Raney Ni, EtOH, reflux, 100%; (k) (i) HC≡C−CH_2OTHP, *n*-BuLi, THF, −78 °C, 6 h, 80%; (ii) PPTS, MeOH, rt, 6 h, 90%; (l) P_2O_5, MsOH (4 equiv), rt, CH_2Cl_2, 1 h, 70%; (m) NaH, THF, rt, 1 h, MeI, 17 h, 75%; (n) di-*tert*-butyl chromate, CCl_4, reflux, 9 h, 80%.

two new chiral centers, the original chiral center was disposed of by converting it into a ketone group. Thus, isomerization of the isopropenyl to isopropylidene group with *p*-toluenesulfonic acid (*p*TSA) converted compound **17** into **18**, $[\alpha]^{25}_D$ +68 (*c* 1.9, $CHCl_3$), which on ozonolytic cleavage generated the diquinane dione **19**, mp 108−110 °C, $[\alpha]^{26}_D$ −42 (*c* 1.2, $CHCl_3$). Controlled thioketalization[8] of dione **19** with



ethanedithiol in the presence of boron trifluoride etherate followed by Raney nickel mediated desulfurization of the resultant monothioketal **20** furnished bicyclic ketone **10**,

(4) Srikrishna, A.; Babu, N. C. *Tetrahedron Lett.* **2001**, *42*, 4913.

(5) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

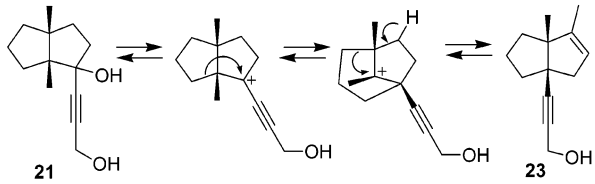
(6) Stork, G.; Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678. Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.

(7) Norin, T. *Acta Chem. Scand.* **1963**, *17*, 738. Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 374 and 2361. Srikrishna, A.; Krishnan, K.; Yelamaggad, C. V. *Tetrahedron* **1992**, *48*, 9725.

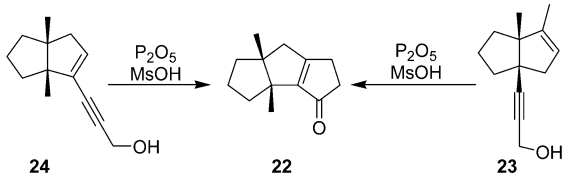
(8) In addition, a small amount (<5%) of the corresponding bis-thioketal (easily separable) was also formed.

$[\alpha]^{26}_D$ −104 (*c* 2.3, $CHCl_3$). A modified Nazarov cyclization was contemplated for the annulation of the third cyclopentane ring.[9] Thus, reaction of ketone **10** with the lithium salt of propargyl THP ether followed by hydrolysis of the THP group furnished diol **21**, mp 98−100 °C, $[\alpha]^{24}_D$ −12.3 (*c* 1.9, $CHCl_3$). After experimenting with different conditions, it was found that treatment of diol **21** directly with Eaton's reagent (15% P_2O_5 in MsOH)[10] in a 0.01 M solution of methylene chloride furnishes triquinane **22**.[11] However, when the reaction was stopped prior to completion, formation of varying amounts of rearranged dehydrated alcohol **23** was observed, in addition to triquinane **22**. The structure of alcohol **23** was deduced from its spectral data.[12] On the other hand, dehydration of mono-THP ether **21a** with pyridine and phosphorus oxychloride followed by hydrolysis of the THP ether generated enynol **24**. Reaction of diol **21** with methanesulfonic acid for a short time resulted in the formation of a 3:1 mixture of alcohols **23** and **24**. Formation of the rearranged alcohol **23** can be readily explained via a series of bond migrations as depicted in Scheme 3.

Scheme 3

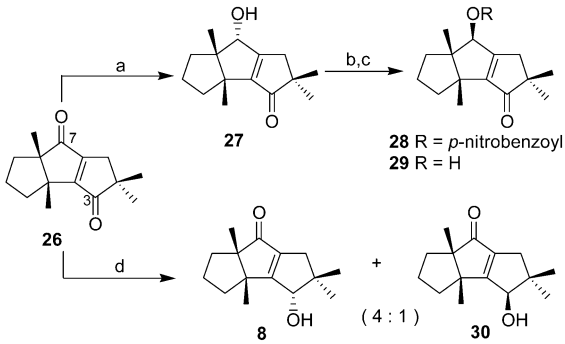


Treatment of enynol **24** with Eaton's reagent furnished triquinane **22**, which is quite expected as it is well established that enynol **24** will be the first intermediate in the **21** → **22** cyclization sequence. But interestingly, even alcohol **23** on treatment with Eaton's reagent furnished triquinane **22**. Formation of triquinane **22** from rearranged alcohol **23** is surprising, as alcohol **23** has to be converted first into enynol **24** for the cyclization to proceed to furnish triquinane enone **22**.



Introduction of the *gem*-dimethyl group by one-step double alkylation transformed enone **22** into enone **25** containing the complete carbon framework of ceratopicanes. Allylic oxidation of enone **25** with di-*tert*-butyl chromate furnished enedione **26** in a highly regioselective manner.[13,14] Regio- and stereoselective reduction of enedione **26** with sodium borohydride−cerium chloride heptahydrate furnished alcohol

Scheme 4[a]



[a] Reagents, conditions, and yields: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 h, 95%; (b) PPh_3, EtOOCN=NCOOEt, *p*-nitrobenzoic acid, THF, rt, 8 h, 85%; (c) K_2CO_3, MeOH, rt, 6 h, 95%; (d) $LiAlH_4$, THF, 0 °C, 5 min, 70%.

(9) Ramaiah, M. *Synthesis* **1984**, 529.

(10) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

(11) All the compounds exhibited spectral data consistent with their structures. Yields refer to isolated and chromatographically pure compounds. Selected spectral data for triquinane **22**: $[\alpha]^{26}_D$ −54 (*c* 1.3, $CHCl_3$). IR (neat) ν_{max}/cm^{-1} 1697, 1646. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 2.70−2.60 (2 H, m), 2.50−2.30 (4 H, m), 2.05−1.97 (1 H, m), 1.70−1.20 (5 H, m), 1.14 (3 H, s), and 1.10 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 202.7 (C), 181.3 (C), 153.3 (C), 56.5 (C), 52.2 (C), 47.6 (CH_2), 44.0 (CH_2), 40.7 (CH_2), 38.2 (CH_2), 25.3 (CH_2), 24.6 (CH_3), 24.0 (CH_2), 20.5 (CH_3). For alcohol **23**: $[\alpha]^{26}_D$ +11.8 (*c* 0.85, $CHCl_3$). IR (neat) ν_{max}/cm^{-1} 3340, 1654. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 5.10 (1 H, br s), 4.25 (2 H, s), 2.63 (1 H, quintet of d, J = 16.5 and 2 Hz), 2.34 (1 H, quintet of d, J = 16.5 and 2 Hz), 2.10−1.90 (1 H, m), 1.82−1.20 (6 H, m), 1.59 (3 H, q, J = 2 Hz), 1.14 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 144.7 (C), 121.1 (CH), 92.7 (C), 80.9 (C), 61.2 (C), 51.5 (CH_2), 49.7 (C), 46.5 (CH_2), 44.0 (CH_2), 37.5 (CH_2), 24.6 (CH_2), 22.9 (CH_3), 13.1 (CH_3). For enynol **24**: $[\alpha]^{24}_D$ −36.5 (*c* 2.6, $CHCl_3$). IR (neat) ν_{max}/cm^{-1} 3341. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 5.84 (1 H, s), 4.37 (2 H, s), 2.30 (2 H, ABq, J = 17.7 Hz), 2.10−1.90 (1 H, m), 1.70−1.20 (6 H, m), 1.04 (3 H, s), 1.03 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 134.9 (CH), 132.7 (C), 88.3 (C), 82.6 (C), 59.7 (C), 51.7 (CH_2), 49.2 (C), 48.5 (CH_2), 44.3 (CH_2), 38.9 (CH_2), 24.8 (CH_3), 23.6 (CH_2), 21.6 (CH_3). For enone **25**: $[\alpha]^{27}_D$ −57 (*c* 1, $CHCl_3$). IR (neat) ν_{max}/cm^{-1} 1698, 1648. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 2.36 (2 H, s), 2.27 (2 H, s), 2.05−1.95 (1 H, m), 1.70−1.20 (5 H, m), 1.14 (3 H, s), 1.11 (6 H, s), and 1.10 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 207.7 (C), 177.9 (C), 150.7 (C), 56.2 (C), 52.5 (C), 50.3 (C), 48.0 (CH_2), 44.3 (CH_2), 42.3 (CH_2), 38.2 (CH_2), 25.7 (CH_3), 25.3 (CH_3), 24.8 (CH_3), 24.3 (CH_2), 20.7 (CH_3). For enedione **26**: $[\alpha]^{24}_D$ −5.3 (*c* 0.95, $CHCl_3$). Mp 88−90 °C. IR (neat) ν_{max}/cm^{-1} 1704. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$) δ 2.45 (2 H, s), 2.00 (2 H, dd, J = 12.9 and 6.3 Hz), 1.65−1.30 (3 H, m), 1.27 (3 H, s), 1.20 (3 H, s), 1.18 (3 H, s), 1.13 (3 H, s), 1.20−0.90 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 210.3 (C), 209.0 (C), 173.5(C), 167.6 (C), 64.7 (C), 51.4 (C), 49.7 (C), 39.7 (CH_2), 36.8 (CH_2), 36.7 (CH_2), 25.5 (CH_3), 25.2 (CH_3), 23.4 (CH_2), 20.1 (CH_3), 19.2 (CH_3). For hydroxyenone **27**: $[\alpha]^{25}_D$ −67 (*c* 0.7, $CHCl_3$). IR (neat) ν_{max}/cm^{-1} 3402, 1680, 1644. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.51 (1 H, br s), 2.45 and 2.26 (2 H, 2 × d, J = 18.3 Hz), 2.16−2.00 (2 H, m), 1.70−1.00 (5 H, m), 1.12 (12 H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$) δ 208.2 (C), 177.3 (C), 150.1 (C), 82.0 (CH), 60.2 (C), 52.3 (C), 50.2 (C), 39.8 (CH_2), 37.8 (CH_2), 34.9 (CH_2), 25.8 (CH_3), 25.0 (CH_3), 24.5 (CH_2), 23.1 (CH_3), 20.6 (CH_3). For epicucumin H **30**: $[\alpha]^{25}_D$ +17 (*c* 1, $CHCl_3$). IR (neat) ν_{max}/cm^{-1} 3421, 1681, 1636. ^1H NMR (300 MHz, $CDCl_3$) δ 4.35 (1 H, s), 2.27 and 2.13 (2 H, 2 × d, J = 15.9 Hz), 1.96 (1 H, dd, J = 12.6 and 5.4 Hz), 1.87 (1 H, dd, J = 11.7 and 5.3 Hz), 1.70−0.90 (5 H, m), 1.27 (3 H, s), 1.12 (3 H, s), 1.11 (3 H, s), and 1.09 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9 (C), 185.4 (C), 146.7 (C), 80.6 (CH), 62.9 (C), 51.3 (C), 47.8 (C), 39.1 (CH_2), 37.8 (CH_2), 36.5 (CH_2), 27.8 (CH_3), 22.9 (CH_2), 22.2 (CH_3), 21.1 (CH_3), 19.3 (CH_3).

(12) The structure of alcohol **23** was further confirmed by the single-crystal X-ray diffraction analysis of the *p*-nitrobenzoate ester of alcohol **23** (CCDC deposition number CCDC 201351)

(13) Kent, G. J.; Wallis, E. S. *J. Org. Chem.* **1959**, *24*, 1235.

(14) A reduction−protection−allylic oxidation−deprotection protocol was also explored for the regiocontrolled conversion of the enone **25** into cucumin H, but was unsuccessful.

27, which is isomeric to cucumin H (**8**). To unambiguously establish the stereochemistry of alcohol in **27**, it was converted into *p*-nitrobenzoate **28** employing a Mitsunobu inversion.[15] The single-crystal X-ray structure[16] of **28** unambiguously established not only the structure of **28** but also the regioselectivity in the allylic oxidation (**25** → **26**) and sodium borohydride (**26** → **27**) reactions. Hydrolysis of

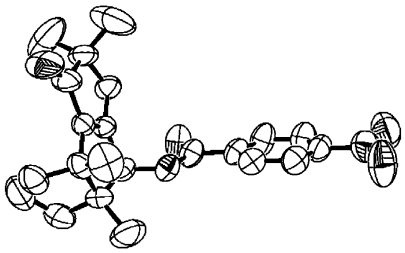


Figure 1. X-ray crystal structure of *p*-nitrobenzoate **28**.

the ester in *p*-nitrobenzoate **28** furnished the corresponding alcohol **29**. Finally, controlled reduction of enedione **26** with lithium aluminum hydride furnished a 4:1 mixture of cucumin H (**8**) and epicucumin H (**30**) via regioselective reduction of the C-3 ketone, which were separated by column chromatography on silica gel. The stereochemistry of the alcohol group in **8** and **30** was ascertained on the basis of the chemical shift due to the C*H*OH signal (δ 4.51 for **8** and δ 4.35 for **30**) in the ^{1}H NMR spectrum in analogy to that in alcohols **27** and **29** (δ 4.51 for **27** and δ 4.33 for **29**). The synthetic sample (−)-**8**, $[\alpha]^{23}_{D}$ −26 (*c* 1, $CHCl_3$) {lit.[2] $[\alpha]^{18}_{D}$ −25 (*c* 1.03, $CHCl_3$)}, exhibited the UV, IR, ^{1}H and ^{13}C NMR (in methanol-d_4), and mass spectra, as well as the sign of the CD curves identical with those of the natural cucumin H, thus confirming the stereostructure of the natural product as well as establishing its absolute configuration.

In conclusion, we have accomplished the first total synthesis of the sesquiterpene (−)-cucumin H (**8**) along with three other regio- and stereoisomers **27**, **29**, and **30**, which in addition to confirming the structure of the molecule also established its absolute configuration. In the process we have observed an interesting reversal in the regioselectivity in the reduction[17] of enedione **26** (C 7 vs C 3 ketones) using sodium borohydride−cerium chloride vs lithium aluminum hydride.

Acknowledgment. We thank Professor Steglich for providing the copies of the spectra (UV, IR, ^{1}H and ^{13}C NMR, mass, and CD) of the natural cucumin H for comparison purposes. We thank the CCD facility of I.I.Sc., Mr. U. Singh for help in the determination of the structure of the *p*-nitrobenzoate of alcohol **23**, and Dr. G. N. Sastry for carrying out the theoretical calculations.

Supporting Information Available: X-ray crystallographic data for compound **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034635P

(15) Hughes, D. L. *Org. React*. **1992**, *42*, 335.

(16) Crystal data for the *p*-nitrobenzoate **28**: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 with use of SHELXL-97. Crystal system monoclinic, space group *P*2(1). Cell parameters: a = 17.449(5) Å, b = 11.559(3) Å, c = 17.582(5) Å, β = 117.88°, V = 3134.85 Å^3, Z = 6, ρ(calcd) = 1.22 g cm^{-3}, F(000) = 1236, μ = 0.09 mm^{-1}, λ = 0.7107 Å. R1 = 0.0524 for 4912 $F_o > 4\sigma(F_o)$ and 0.0875 for all 7649 data. *w*R2 = 0.1228, GOF = 0.878. There are three independent molecules in the asymmetric unit. An ORTEP drawing of compound **28** with a 50% ellipsoidal probability level is shown in Figure 1 (only one molecule is shown and hydrogen atoms are removed for clarity). Crystallographic data are being deposited with the Cambridge Crystallographic Data Center (CCDC 201351)

(17) Theoretical calculations (MNDO and AM1 level) indicated that exo sides of both the C 3 and C 7 ketones in **26** are equally preferred for the hydride attack, which is followed by the endo face of the C 3 ketone, whereas the endo face of the C 7 ketone is hindered for the hydride attack. However, the origin of the total difference in regioselectivity between the sodium borohydride−cerium chloride and lithium aluminum hydride in the reduction of **26** is not clear.