JOC*Article*

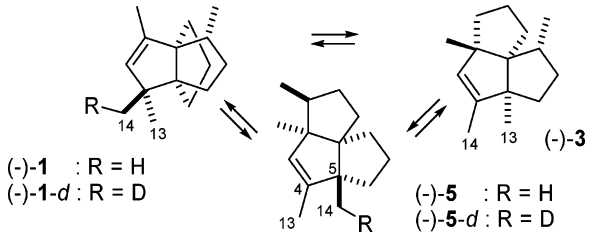
Molecular Rearrangements of (−)-Modhephene and (−)-Isocomene to a (−)-Triquinane

Pedro Joseph-Nathan,[†] Benito Reyes-Trejo,[‡] and Martha S. Morales-Ríos*,[†]

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México, D. F., 07000 México, and Laboratorio de Productos Naturales, Área de Química, Universidad Autónoma Chapingo, Apartado 74, Oficina de Correos Chapingo, Texcoco, México, 56230 México

smorales@cinvestav.mx

Received February 7, 2006



The preparation and further rearrangement of (−)-modhephene (**1**) to a (−)-triquinane **5** has been assessed through acid catalysis. The rearrangement involved protonation, 1,2 σ-bond and methyl shifts, and deprotonation. Monitored experiments by ^{1}H NMR spectroscopy suggested the intermediate (−)-isocomene (**3**), which was further evidenced when a sample of natural (−)-**3** undergoes acid-catalyzed conversion to the (−)-triquinane **5**. In addition, deuterated (−)-modhephene (**1**-*d*) labeled stereospecifically at the 14β geminal methyl group at C4 was synthesized, through the corresponding chiral deuterated primary alcohol, in 5 steps, starting from natural (−)-14-hydroxymodhephene (**8**), and rearranged under acid catalysis to elucidate the stereochemical factors that control the methyl shift at this position. The final deuterium-labeled (−)-triquinane, **5**-*d*, obtained from [14-^{2}H$_1$]-**1**-*d* was established to have deuterium in the methyl group at C5 by ^{13}C NMR spectroscopy. This stereoselective methyl migration is in accordance with the molecular orbital demand formulated by the quantum chemical calculations performed in the present study.

Introduction

A small class of tricyclopentenoid compounds known as triquinanes have received considerable attention in recent years as a result of their unique architecture, which presents significant synthetic challenges as well as a wide range of biological activity exhibited by some of them.[1] Although triquinanes are found in relatively abundant plants, they are present in only minute amounts as complex volatile mixtures of structurally similar isomers, thus, isolation of the pure components represents a major challenge. (−)-Modhephene (**1**), isolated from *Isocoma wrigthii*,[2] (Chart 1) was the first reported triquinane possessing the [3.3.3]propellane nucleus. The relative structure of (−)-**1** was determined by single-crystal X-ray analysis of a derived diol,[2a] and the absolute stereochemistry was established through the stereospecific rearrangement of (+)- and (−)-dispiroundecanol **2**.[3] From *Isocoma wrigthii* was also isolated (−)-isocomene (**3**),[4] a triquinane possessing a cyclopenta[c]pentalene framework.

(−)-Modhephene (**1**) has been the subject of a number of total racemic, diasteroselective, and enantioselective syntheses.[5] Within the strategies used, a new approach involves cationic cascade rearrangements of (±)-dispiroundecanol **2**.[6] Under

[†] Centro de Investigación y de Estudios Avanzados del IPN.
[‡] Universidad Autónoma Chapingo.

(1) (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719. (b) Dobner, M. J.; Schwaiger, S.; Jenewein, I. H.; Stuppner, H. *J. Ethnopharmacol*. **2003**, *89*, 301−303.

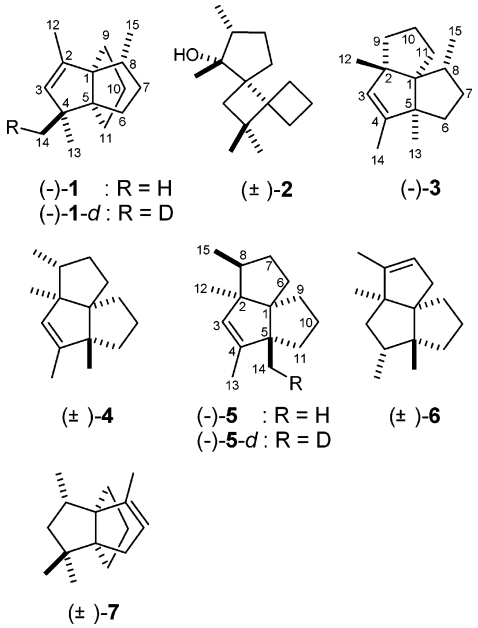
(2) (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D. *J. Chem. Soc., Chem. Commun.* **1978**, 420−421. (b) Bohlmann, F.; Zdero, C.; Bohlmann, R.; King, R. M.; Robinson, H. *Phytochemistry* **1980**, *19*, 579−582.

(3) Fitjer, L.; Monzó-Oltra, H.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1492−1494.

(4) (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456−457. (b) Bohlmann, F.; Le Van, N.; Pickardt, J. *Chem. Ber*. **1977**, *110*, 3777−3781.

10.1021/jo060258t CCC: $33.50
Published on Web 05/16/2006

CHART 1



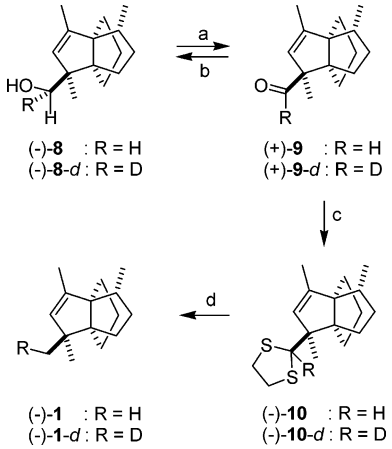
kinetic control, the Wagner−Meerwein cascade reactions of (±)-**2** gave (±)-modhephene (**1**) and a (±)-triquinane **4** in a ratio 2:1. Whereas, under thermodynamic control, (±)-**2** was rearranged into (±)-isocomene (**3**), (±)-triquinanes **4**−**6**, and the (±)-propellane **7** in a ratio 7:8:5:2:2, respectively. In addition, it has been proposed that (±)-**1** may formally rearrange to (±)-**3** by three consecutive 1,2 shifts and to triquinane (±)-**5** by seven 1,2 shifts, in which the last comprises a 1,2-methyl migration.[6]

Recently, we reported the isolation and stereostructural characterization of a new hydroxyl derivative of (−)-**1**, the (−)-14-hydroxymodhephene **8** from *Pluchea sericea* roots.[7a] Our interest in the latter compound arises from the fact that it could be advantagely transformed into (−)-**1**. To get experimental evidence concerning the acid-catalyzed conversion of (−)-**1** to (−)-triquinane **5**, protio and deuterated isotopomers of (−)-**1** were prepared. Herein, we provide an account of an efficient method for the stereoselective labeling of the 14*β* geminal methyl group at C4 of (−)-modhephene (**1**), using a previously described protocol to insert deuterium at the neopentylic position in cedrene derivatives,[8] with the aim to elucidate the stereochemical factors that control the 1,2-methyl migration. In addition, we used a semiempirical PM3 method[9] to obtain the total energies of the cationic intermediates proposed to be formed in the rearrangement of (−)-modhephene (**1**).

Results and Discussion

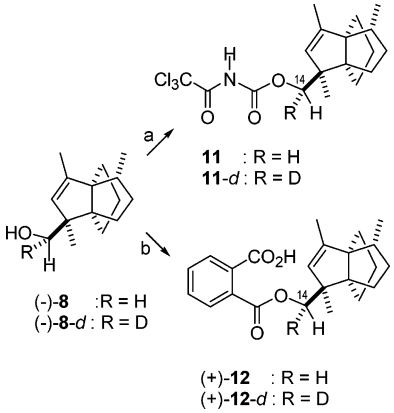
Preparation of Protio and Deuterated Isotopomers of (−)-Modhephene (1). The syntheses of (−)-**1** and [14-$^2H_1$]-(−)-**1** are shown in Scheme 1. Starting from natural (−)-14-hydroxymodhephene **8**, (−)-**1** was synthesized, employing a convenient selective oxidation/sulfur acetalization/reductive desulfurization sequence. The first step was the selective oxidation of neopentylic alcohol (−)-**8** with the complex CrO_3−Py_2. The oxidation was performed with 93% isolated yield of (+)-**9**, which underwent sulfur acetalization by treatment with 1,2-ethanedithiol and anhydrous $CuSO_4$ to give (−)-**10** in 62% yield. Finally, Raney-Ni-catalyzed reductive desulfurization of (−)-**10** gave (−)-**1** in 80% yield.

SCHEME 1 [a]



[a] Reagents: (a) CrO_3−Py_2, CH_2Cl_2; (b) $NaBD_4$, MeOD; (c) anhydrous $CuSO_4$, $(CH_2SH)_2$, benzene; (d) Raney-Ni, EtOH.

SCHEME 2 [a]



[a] Reagents: (a) CCl_3CONCO; (b) phthalyc anhydride, toluene.

Additionally, using the same methodology, [14-$^2H_1$]-(−)-**1** was synthesized from aldehyde (+)-**9** (Scheme 1). First, the reduction of (+)-**9** with $NaBD_4$ to give (−)-**8**-*d* was accomplished in 79% yield. Compounds (+)-**9**-*d*, (−)-**10**-*d*, and (−)-**1**-*d* were then prepared, analogously to protio isotopomers (+)-**9**, (−)-**10**, and (−)-**1**, in 88, 64, and 75% yields, respectively.

The deuterium content of (−)-**8**-*d*, determined in the trichloroacetyl isocyanate (TAI) derivative **11**-*d*,[10] after being treated in situ by the addition of TAI (Scheme 2), was 91 ± 1%. Whereas, for the oxidized product (−)-**9**-*d*, the isotope effect leads to a deuteration degree greater than 78%, as determined by ^1H NMR peak areas.

(5) (a) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1−163. (b) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467−1486. (c) Ramaiah, M. *Synthesis* **1984**, 529−570. (d) Lee, H.-Y.; Moon, D. K.; Bahn, J. S. *Tetrahedron Lett.* **2005**, *46*, 1455−1458.

(6) Fitjer, L.; Majewski, M.; Monzó-Oltra, H. *Tetrahedron* **1995**, *51*, 8835−8852.

(7) (a) Reyes-Trejo, B.; Joseph-Nathan, P. *Phytochemistry* **1999**, *51*, 75−78. (b) Reyes-Trejo, B.; Morales-Ríos, M. S.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Magn. Reson. Chem.* **2003**, *41*, 1021−1025.

(8) Joseph-Nathan, P.; Santillán, R. L.; Gutiérrez, A. *J. Nat. Prod.* **1984**, *47*, 924−933.

(9) Stewart, J. J. P.; Davis, L. P.; Burggraf, L. W. *J. Comput. Chem.* **1987**, *8*, 1117−1123.

(10) Samek, Z.; Budesinsky, M. *Collect. Czech. Chem. Commun.* **1979**, *44*, 558−588.

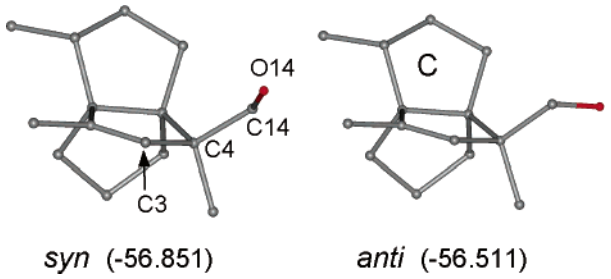


FIGURE 1. Minimal energy conformations of syn (∠C3−C4−C14−O14 = 11.21°) and anti (∠C3−C4−C14−O14 = 163.48°) rotamers of (+)-**9** (hydrogen atoms omitted for clarity) calculated at the PM3 level of theory. The values in parentheses are the total energies in kcal/mol. Boltzmann populations correspond to a ratio of ca. 2:1 in favor of the syn conformer.

The good diastereoselectivity (dr 9:1) in the reduction of (+)-**9** with $NaBD_4$ to afford (−)-**8**-*d* was determined on the basis of ^1H NMR analysis of the corresponding TAI derivative **11**-*d* (see Supporting Information, S17). This result suggests that the reaction benefits from conformational control and specific steric effects. Although the π-facial stereoselectivity in nucleophilic additions to β,γ-unsaturated carbonyl compounds may be also controlled by electrostatic effects,[11] in this case, evidence of the homoconjugation[12] between the aldehyde carbonyl group and the C2═C3 double bond of β,γ-unsaturated aldehyde (+)-**9** was obtained from the UV spectrum, which exhibits a characteristic absorption band at 220 nm (ϵ_{max} 2300), assigned to the $\pi-\pi^*$ transition, allowing significant stabilization of the syn-oriented carbonyl conformer with respect to the anti conformer. The initial Monte Carlo conformational search of (+)-**9** reveals the existence of four structures, two of which are produced by a rotation at the C4−C14 bond, with relative energies (ΔG) of 0 (reference value) and +0.381 kcal/mol. The remaining two higher-energy species, +3.626 and +4.466 kcal/mol, result from a conformational change in the propellane C ring.[13] The PM3 geometry optimizations of the two lower-energy conformations, produced by rotation of the C4−C14 bond, corresponding to the syn and anti conformers, show C3−C4−C14−O14 dihedral angles of 11.21° and 163.48°, respectively. On the basis of the depicted geometries in Figure 1, it is clear that for the lowest-energy syn conformer, the C-ring effectively blockades the re face of the carbonyl group for deuteride attack, which in consequence occurs from the less-stereohindered si face to give (−)-**8**-*d* in the (14*S*)-configuration. In this regard, controlled selectivity of metal deuteride reductions of aldehydes to afford chiral deuterated primary alcohols has been induced until now by the use of chiral reagents.[14a−f]

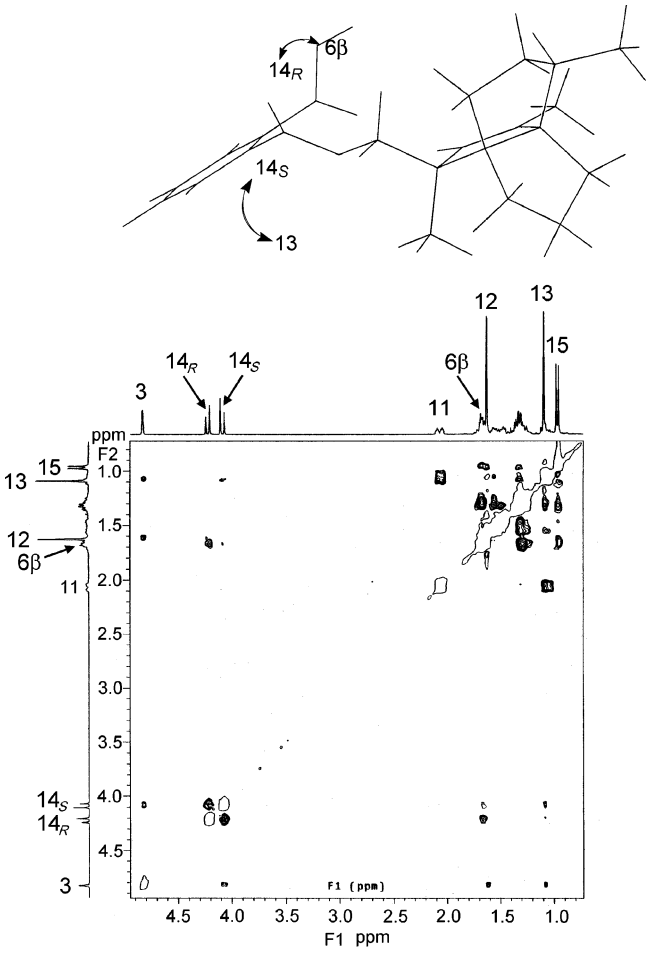


FIGURE 2. Minimal energy conformation of (+)-**12**, calculated at the PM3 level of theory, and a two-dimensional NMR plot showing NOESY correlations.

The absolute stereochemistry at C14 for the major diastereomer (−)-**8**-*d*, assigned as 14*S*, was established by the study of the derived hemiphthalate (+)-**12**-*d* (Scheme 2). A detailed evaluation of the NOESY correlations of the protio hemiphthalate derivative (+)-**12** allowed a distinction between the prochiral methylene protons. Thus, pro-*S* H14 gives a cross-peak with the methyl group on C4, whereas pro-*R* H14 shows a cross-peak with H6β. These results are diagnostic of a priority conformation in solution, which is coincident with that obtained by molecular modeling (Figure 2) and by X-ray diffraction analysis.[7b] The NMR study of (+)-**12**-*d* clearly indicates the (14*S*)-configuration of its precursor (−)-**8**-*d*.

Precise measurements of the ^{13}C NMR spectra of (−)-**1**-*d* demonstrate the presence of a mixture of isotopically labeled (CH_2D) and unlabeled (CH_3) species. The triplet CH_2D signal of C14 showed a $^1J(^{13}C,D)$ of 19 Hz and was shifted to low frequency by 0.307 ppm (307 ppb) with respect to the singlet of the CH_3 species, in accord with isotopic-induced shifts for methyl groups[15] (Figure 3). These data allowed to reassign the geminal methyl resonances at C4 for (−)-**1**.[7a]

Acid-Catalized Conversion of (−)-Modhephene (1) to (−)-Triquinane 5. The equilibration experiments were done by refluxing solutions of (−)-**1** (0.59 mmol) in benzene containing

(11) Fujita, M.; Akimoto, S.; Ogura, K. *Tetrahedron Lett.* **1993**, *34*, 5139−5142.

(12) (a) Baggiolini, E.; Hamlow, H. P.; Schaffner, K. *J. Am. Chem. Soc.* **1970**, *92*, 4906−4921. (b) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 2479−2482. (c) Sato, F.; Takeda, Y.; Uchiyama, H.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1132−1134.

(13) For a detailed description of [3.3.3]propellane conformers, see: Krivdin, L. B. *Magn. Reson. Chem.* **2004**, *42*, 1−13.

(14) For the preparation of chiral deuterated primary alcohols by the enantioselective deuteride reduction of aldehydes, see: (a) Miyazaki, D.; Nomura, K.; Ichihara, H.; Ohtsuka, Y.; Ikeno, T.; Yamada, T. *New J. Chem.* **2003**, *27*, 1164−1166. (b) Xu, L.; Price, N. P. J. *Carbohydr. Res.* **2004**, *339*, 1173−1178. (c) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425−3427. (d) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275−6278. (e) Keck, G. E.; Krishnamurthy, D. *J. Org. Chem.* **1996**, *61*, 7638−7639. (f) Dupre, M.; Gaudemer, A. *Tetrahedron Lett.* **1978**, *31*, 2783−2786.

(15) Morales-Ríos, M. S.; Cervantes-Cuevas, H.; Salgado-Escobar, I.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1999**, *37*, 243−245.

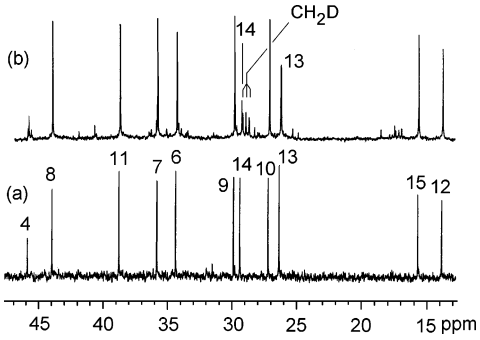


FIGURE 3. ^{13}C NMR (75 MHz, $CDCl_3$) spectra of (a) (−)-**1** and (b) (−)-**1**-*d*.

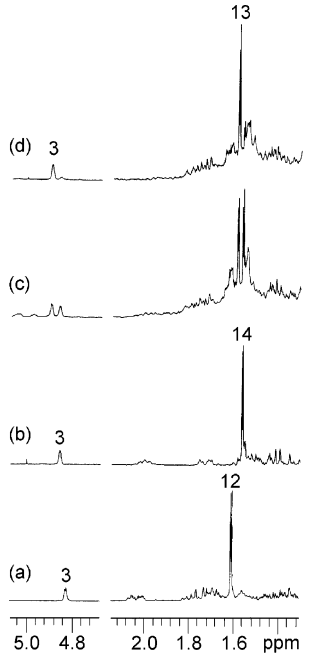


FIGURE 4. Partial ^1H NMR (300 MHz, $CDCl_3$) spectral change of (−)-**1** (0.59 mmol) upon the addition of TsOH (0.58 mmol) in refluxing benzene (a) before adding TsOH, (b) of the natural (−)-isocomene (**3**), (c) after reacting for 30 min, (d) and after reacting for 90 min.

1 equiv of TsOH. Due to signal overlap, not all the regions of the ^1H NMR spectrum are convenient for monitoring the Wagner−Meerwein-type rearrangements. However, the remoteness of the vinylic H3 and Me signals of (−)-**1**, (−)-**3**, and (−)-**5** from other signals and their spread (**1**,[2b] **3**,[4b] and **5**[6]) enables their unequivocal identity.

When the equilibration reaction of (−)-**1** was quenched with saturated aqueous $NaHCO_3$ (3 mL), after 30 min the resulting (−)-isocomene **3** and (−)-triquinane **5** were observed in about equal proportion and (−)-**1** was completely consumed, as inferred from the ^1H NMR analysis of the reaction mixture. The use of a longer reaction time (90 min), resulting in thermodynamic reaction conditions, yielded (−)-triquinane **5** as the sole product. Figure 4 shows the ^1H NMR spectral changes with time observed for the vinylic proton and methyl signals in (−)-**1** upon addition of 1 equiv of TsOH. Control experiments from natural (−)-**3** showed that its total conversion to (−)-**5** occurs in about 90 min, demonstrating that the (−)-triquinane **5** is produced from the rearrangement of both (−)-modhephene (**1**) and (−)-isocomene (**3**). These results are in agreement with the report of Fitjer et al.[6] However, the question that arises is which of the geminal methyl groups of (−)-**1** are being rearranged. For this purpose, computational and stereochemical deuterium-labeling studies were conducted, which are subsequently described.

Computational Studies. The stationary structures and products were obtained by geometry optimization, without symmetry constraint at the semiempirical PM3 level of calculations, using a SPARTAN 04 package. Harmonic frequency analysis was used to confirm all structures as stationary points. The initial conformational searches were performed with Monte Carlo calculations.

The stepwise mechanism for the rearrangement of (−)-**1** to (−)-**5** has been proposed by Fitjer et al.[6] to account through five 1,2 σ-bond shifts and an epimerization through a bridgeheaded olefin[16] as the bifurcation point.[17] To have further insight into the molecular rearrangement of (−)-**1**, theoretical studies were carried out on the stationary structures of the possible carbenium ion intermediates **13**−**21** (Figure 5). Thus, relative energies, geometrical features, and hyperconjugative stabilization in the corresponding carbenium ions, not previously described, have been examined and compared.

As shown in Figure 5, the first step of the rearrangement is the protonation of (−)-**1** at the C3, generating the stabilized tertiary cation **13**, which in turn undergoes a C1−C9 bond shift, producing the less-stable bridgehead cation **14** (Table 1). At this point, two energy paths are possible through the intermediate cation **14** (paths I and II in Figure 5). In path I, the higher-energy cation **15**, formed by the epimerization of cation **14**, is rearranged into the more-stable cation **16** by a C2−C9 bond shift. The cation **17** is formed by a C1−C8 bond migration from cation **16** and is 10.50 kcal/mol less stable than cation **16**. Then, cation **17** gives rearranged cation **18** by C5−C6 bond shift, being more stable than cation **17** by 7.45 kcal/mol. The specific 1,2 migration of C14β leads to the final cation intermediate **19**, which appears to be the most stable. The terminating proton abstraction removes H3β from cation **19**, in agreement with calculations, as detailed below, forming (−)-triquinane **5**. The whole molecular rearrangement (−)-**1** → (−)-**5** has an enthalpy of −1.95 kcal/mol. Alternatively,[16] in path II (Figure 5), the common cation **14** is rearranged into cation **20** by a C5−C11 bond shift that lies 6.83 kcal/mol lower in energy than **14**. The specific 1,2 migration of C13α leads to cation intermediate **21**, which appears to be energetically favorable by 3.47 kcal/mol. This cation **21** leads to (−)-**3** by an H3α elimination. The reversibility of the process leads to the final product (−)-**5**, which is the global minimum of this system (Table 1).

Stereospecific 1,2-Methyl Migration: Deuterium Experiments. The elucidation between which of the geminal methyl groups of cations **18** and **20** are being rearranged should be possible by means of deuterium-labeled substrates in combination with the stereoelectronic requirement of the Wagner−Meerwein-type rearrangements. The stereochemical deuterium-labeling equilibration studies were performed by refluxing a benzene solution of [14-$^2H_1$]-**1**-*d*, prepared following the sequence depicted in Scheme 1, with 1 equiv of TsOH. The

(16) Although molecular modeling indicates that a direct 1,3-alkyl shift for cation **13** is stereoelectronically favorable to give **20** in path II, the postulated process through the higher-energy cation **14**, mediated by two consecutive 1,2-alkyl shifts, is required to account for the Me15α → Me15β isomerization to afford cation **15** in path I.

(17) (a) Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 5525−5528. (b) Fitjer, L.; Monzó-Oltra, H. *J. Org. Chem.* **1993**, *58*, 6171−6173.

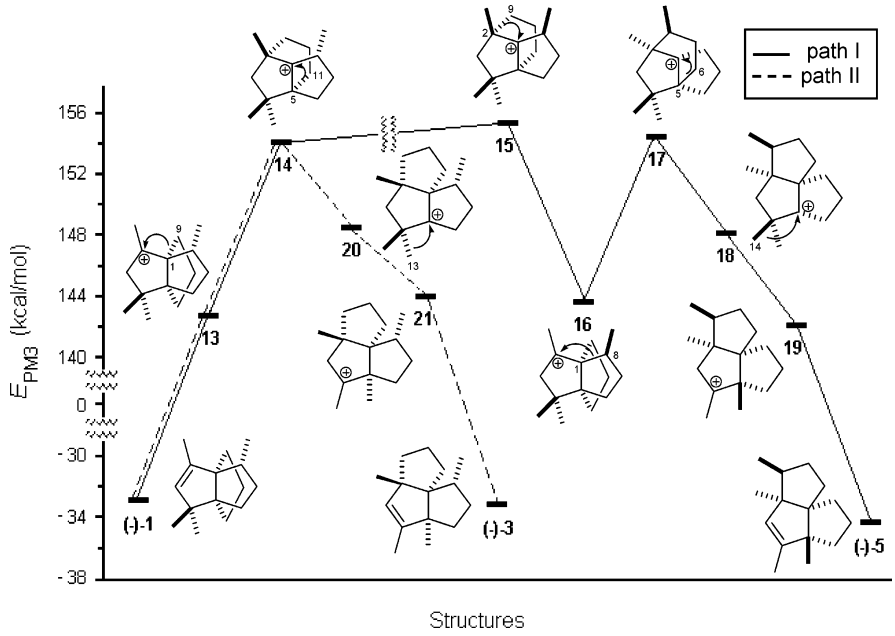


FIGURE 5. Total energies (kcal/mol) for cations **13**−**21** proposed to be formed through 1,2 σ-migrations (paths I and II) in the equilibration reactions of (−)-**1** → (−)-**5** calculated at the PM3 level of theory.

TABLE 1. Total and Relative Energies[a] (kcal/mol) for the Carbocations and Neutral Molecules (given in Figure 5) Involved in Paths I and II

	E_{PM3}	$G°$	ΔG[b]		E_{PM3}	$G°$	ΔG
13	142.451	347.733	+0.428	**19**	141.762	347.304	0
14	153.769	359.333	+12.028	**20**	148.336	352.495	+5.191[b]
15	154.872	359.914	+12.610	**21**	144.039	349.028	+1.724[b]
16	143.450	349.034	+1.730	**1**	−32.931	168.202	+2.410[c]
17	154.203	359.536	+12.232	**3**	−33.469	166.630	+0.838[c]
18	147.921	352.091	+4.786	**5**	−34.256	165.792	0

[a] Optimized geometries at PM3. [b] Relative to cation **19**. [c] Relative to **5**.

deuterium-labeling studies clearly disclose that the acid-catalyzed rearrangement of (−)-**1**-*d* gave the [14-$^2H_1$]-(−)-triquinane **5**-*d* after 90 min of reaction. The selected isotopically shifted peak of the 14βCH_2D group in the ^{13}C NMR spectrum of (−)-**5**-*d* provided evidence that this group is transferred stereospecifically from C4 to the angular 5β-position of product (−)-**5**-*d*, indicating that the fraction of the reaction that proceeds through path I is relevant. The triplet signal of the 14βCH_2D group showed a $^1J(^{13}C,D)$ of 19 Hz and was shifted to low frequency by 0.303 ppm with respect to the singlet of the unlabeled species (Figure 6).

The observed stereospecific rearrangement of the 14βCH_2D group indicates the likelihood of a stereoelectronically favorable antiperiplanar 1,2-migration step, that is, the migrating σ-bond should be perpendicular to the plane of the sp^2 cation carbon. At this point, it would be important to stress that molecular modeling indicates that, for cation structure **18**, the dihedral angle composed by the migrating σ-bond and the plane of the sp^2 cation carbon is within the range of 90 to 102° (∠C14−C4−C5−C1 and ∠C14−C4−C5−C11, Table 2), in good accordance with the molecular orbital demand and experimental findings. In addition, in cation **19**, a noticeable dihedral angle difference was observed between H3β−C3−C4−C13 (73.81°) and H3α−C3−C4−C13 (39.35°) or between H3β−C3−C4−C5 (−107.80°) and H3α−C3−C4−C5 (139.04°), indicating that proton elimination forming (−)-**5** must occur on the β-face.

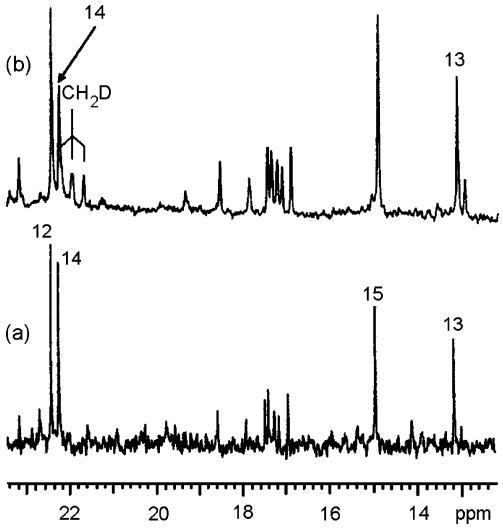


FIGURE 6. Partial ^{13}C NMR (75 MHz, $CDCl_3$) spectra of (a) unlabeled (−)-triquinane **5** and (b) [14-$^2H_1$]-(−)-triquinane **5**-*d*, obtained by the rearrangement of [14-$^2H_1$]-(−)-modhephene (**1**-*d*).

A parallel finding shows that isocomene (−)-**3** derived from (−)-**1**-*d* does not show any noticeable deuterium content on methyl carbons C13 or C14, as deduced from the ^1H NMR spectrum obtained after reacting for 30 min. Apparently, the loss of deuterium occurs from the hyperconjugated stabilized cation structure **21**-*d* through a scrambling with the medium, according to path II. Information about a possible isotope effect[18] on the relative amounts of (−)-**3** and (−)-**5** was also obtained when the equilibration reaction of (−)-**1**-*d* was quenched after 30 min. The increased proportion of (−)-**5** was established by the integration of the vinylic H3 signals in the ^1H NMR spectrum of the reaction mixture. Effectively, the (−)-**3**/(−)-**5** ratio was 2:3 in contrast to the about equal proportion observed

(18) Vrèek, V.; Saunders, M.; Kronja, O. *J. Org. Chem.* **2003**, *68*, 1859−1866.

TABLE 2. Comparison of Relevant Dihedral Angles (∠) for Cations 18−21 Calculated at the PM3 Level of Theory

18 ∠ (deg)	**19**∠ (deg)	**20** ∠ (deg)	**21** ∠ (deg)
C14−C4−C5−C1 = 101.96	H3β−C3−C4−C5 = −107.80	C14−C4−C5−C1 = −133.00	H3β−C3−C4−C5 = −132.76
C14−C4−C5−C11 = 89.68	H3β−C3−C4−C13 = 73.81	C14−C4−C5−C6 = 37.11	H3β−C3−C4−C14 = 44.98
C13−C4−C5−C1 = −136.69	H3α−C3−C4−C5 = 139.04	C13−C4−C5−C1 = 106.01	H3α−C3−C4−C5 = 114.20
C13−C4−C5−C11 = −31.67	H3α−C3−C4−C13 = −39.35	C13−C4−C5−C6 = −83.87	H3α−C3−C4−C14 = −68.06

TABLE 3. Relevant Bond Lengths (Å) and Bond Orders (in Parentheses) for Carbocations 13, 16, 19, and 21

cation	C2−C12	C4−C13	C4−C14	C8−C15
13	1.445 (1.102756)	1.520 (0.985944)	1.528 (0.984264)	1.509 (0.995994)
16	1.445 (1.104236)	1.529 (0.984167)	1.523 (0.985716)	1.515 (0.994287)
19	1.523 (0.986825)	1.449 (1.094106)		1.514 (0.993996)
21	1.522 (0.986655)		1.448 (1.096004)	1.520 (0.992799)

for the corresponding nondeuterated counterpart (see Figure 4). This result implies that the less "kinetically acidic" deuterium atom gave rise to an attenuation in the formation of (−)-isocomene (**3**).

Molecular modeling indicates the likelihood of a stereoelectronically favorable alignment of the 13αMe group with the sp^2 carbon cation in the calculated cation structure **20** (Table 2), to generate the hyperconjugated stabilized intermediate cation **21** by vicinal 13αMe rearrangement from C4 to C5, in agreement with experimental data. In the case of cation **21**, H3α shows a better geometrical disposition for elimination than H3β to give (−)-**3** (Table 2). The hyperconjugative stabilization of cations **13**, **16**, **19**, and **21** is corroborated by the fact that the C^+−Me bond lengths are shorter than in the neutral Csp^3—Me bonds (Table 3), reflecting the strength of the π interactions between the methyl substituent and the empty p orbital on the cation center (see bond orders in Table 3).

Conclusions

Starting from natural (−)-14-hydroxymodhephene (**8**), we synthesized and characterized modhephene (−)-**1** and [14-$^2H_1$]-(−)-**1** by the application of a selective oxidation/sulfur acetalization/reductive desulfurization sequence. The stereoselective 1,2-methyl migration in the rearrangement of (−)-**1** to isocomene (−)-**3** and triquinanne (−)-**5** was assessed by stereospecific labeling of the 14β geminal methyl group of (−)-**1**. The $NaBD_4$ reduction of (+)-modhephen-14-al (**9**) to the corresponding deuterated primary alcohol (14*S*)-(−)-**8**-*d* provides the first example of a high diastereoselective $NaBD_4$ reduction involving a β,γ-unsaturated aldehyde, without an added chiral reagent. In this reduction, the resident stereogenic centers could exhibit modest stereoinduction, leading to the stereohindered re-face-controlled selectivity. Isotope effects demonstrated that the major reaction route to triquinane (−)-**5** is that presented as path I, and the fraction of the reaction that proceeds through path II can be rationalized if an epimerization step occurs at the stage of cation **14**. In addition, the stereospecific mechanisms of the 1,2-methyl shifts and the terminating proton eliminations were investigated using the PM3 semiempirical method.

Experimental Section

(+)-Modhephen-14-al (9). To a stirred solution of CH_2Cl_2 (35 mL) and anhydrous pyridine (2.3 mL, 27 mmol) at 5 °C was added CrO_3 (1.4 g, 14 mmol), and the stirring was continued for 1 h at 25 °C. After the addition of alcohol (−)-**8** (0.5 g, 2.25 mmol) in CH_2Cl_2 (5 mL), the mixture was stirred at the same temperature for an additional 5 min. The mixture was filtered through a pad of silica gel (20 g), and the pad was washed with CH_2Cl_2 (100 mL). The filtrate and washings were combined, washed with 10% HCl (2 × 25 mL), H_2O (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and H_2O (25 mL), dried (Na_2SO_4), and evaporated under vacuum to leave a yellow oily residue, which was purified by chromatography on silica gel (hexane) to give (+)-**9** (461 mg, 93%) as a colorless oil: $[\alpha]^{20}_{589}$ +130, (*c* 1.30, $CHCl_3$), $[\alpha]^{20}_{578}$ +136, $[\alpha]^{20}_{546}$ +164, $[\alpha]^{20}_{436}$ +391, $[\alpha]^{20}_{365}$ +1140; UV (EtOH, ϵ) λ_{max} 220 (2300); IR ($CHCl_3$) ν_{max} 3030, 2948, 2866, 1712, 1628, 1468, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, H14), 4.90 (q, J = 1.4 Hz, 1H, H3), 2.12 (m, 1H, H11), 1.84−0.98 (m, 10H, 5 × CH_2), 1.73 (d, J = 1.4 Hz, 3H, H12), 1.11 (m, 1H, H11′), 1.10 (s, 3H, H13), 1.02 (d, J = 6.5 Hz, 3H, H15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5 (C14), 148.3 (C2), 125.8 (C3), 73.7 (C1), 65.7 (C5), 62.0 (C4), 43.2 (C8), 38.0 (C11), 35.4 (C7), 35.1 (C6), 29.7 (C9), 26.9 (C10), 17.3 (C13), 15.4 (C15), 14.1 (C12). EIMS (20 eV) *m*/*z*: 218 (M^+, 0.1), 189 (100), 187 (19.5).

(−)-Modhephen-14-ethylenedithioacetal (10). To a stirred solution of (+)-modhephen-14-al (**9**; 480 mg, 2.2 mmol) and 1,2-ethanedithiol (0.85 mL, 1.0 g, 10.6 mmol) in anhydrous benzene (20 mL) was added anhydrous $CuSO_4$ (840 mg, 5.3 mmol). The resulting mixture was refluxed for 2 h, quenched by the addition of ice water (20 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with cold 10% NaOH solution (12 × 25 mL) and H_2O (2 × 25 mL), dried (Na_2SO_4), filtered, and evaporated under vacuum to leave a whitish oily residue, which was purified by chromatography on silica gel (hexane) to give (−)-**10** (403 mg, 62%) as a colorless oil: $[\alpha]^{20}_{589}$ −45, (*c* 3.2, $CHCl_3$), $[\alpha]^{20}_{578}$ −47, $[\alpha]^{20}_{546}$ −53, $[\alpha]^{20}_{436}$ −86, $[\alpha]^{20}_{365}$ −120; IR ($CHCl_3$) ν_{max} 3016, 2952, 2868, 1522, 1474, 1426 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (q, J = 1.4 Hz, 1H, H3), 4.77 (s, 1H, H-14), 3.15 (m, 4H, H16, H16′, H17, H17′), 2.12 (m, 1H, H11), 1.84−1.04 (m, 10H, 5 × CH_2), 1.62 (d, J = 1.4 Hz, 3H, H12), 1.22 (s, 3H, H13), 1.09 (m, 1H, H11′), 0.98 (d, J = 6.5 Hz, 3H, H15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (C2), 132.3 (C3), 73.4 (C1), 67.5 (C5), 64.2 (C14), 55.2 (C4), 43.2 (C8), 39.2 (C16), 39.0 (C17), 38.7 (C11), 36.0 (C7), 35.3 (C6), 27.6 (C10), 30.6 (C9), 17.7 (C13), 15.4 (C15), 13.8 (C12). CIMS (20 eV) *m*/*z*: 295 (M^+ + H, 100), 201 (39), 189 (10); HRCIMS calcd for $C_{17}H_{27}S_2$, 295.1554 (M^+ + H); found, 295.1550.

(−)-Modhephene (1). To a solution of dithioacetal (−)-**10** (90 mg, 0.31 mmol) in absolute ethanol (15 mL) was added Raney nickel (1.0 g), and the solution was refluxed for 5 h. The mixture was filtered through a pad of Celite (10 g), and the pad was washed with ethanol (4 × 20 mL). The filtrate and washings were combined and concentrated under reduced pressure to give an oily residue, which was purified by chromatography on $AgNO_3$-impregnated[19] silica gel (20%, w/w), using hexane as the eluent to afford (−)-**1** (50 mg, 80%) as a colorless oil. The spectral data of (−)-**1** were identical with those reported,[2b,7a] except the reassignment of the ^{13}C NMR signals at δ 26.3 (C13) and 29.3 (C14).

[14-$^2H_1$]-(−)-14-Hydroxymodhephene (8-*d*). To a stirred solution of aldehyde (+)-**9** (50 mg, 0.23 mmol) in MeOD (2 mL, 93% D) at 0 °C was added $NaBD_4$ (5 mg, 0.12 mmol, 98% D). The reaction mixture was allowed to stir at the same temperature for 5

(19) Jin, Q.; Williams, D. C.; Hezari, M.; Croteau, R.; Coates, R. M. *J. Org. Chem.* **2005**, *70*, 4667−4675.

min, quenched with ice water (2 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to dryness to give an oily residue. The residue was purified by chromatography on silica gel (hexane) to afford (−)-**8**-*d* as an inseparable epimeric mixture with a 14*S*/14*R* selectivity of 9:1 (40 mg, 79%). The major compound exhibited an identical ^{1}H NMR spectrum to that of (−)-14-hydroxymodhephene (**8**), except for the integrated peak area corresponding to the primary alcohol methylene signals at δ 3.30 and δ 3.41.[7b] The deuterium content was determined to be 91 ± 1% on the basis of the ^{1}H NMR analysis of the corresponding TAI derivative **11**-*d*.

[14-^{2}H$_1$]-(+)-Modhephen-14-al (9-*d*). Compound (−)-**8**-*d* (250 mg, 1.13 mmol) was oxidized with the complex CrO_3−Py_2 (700 mg, 7 mmol) by the same procedure used in the preparation of (+)-**9** to give (+)-**9**-*d* (218 mg, 88%) as a clear oil. The title compound exhibited an identical ^{1}H NMR spectrum to the unlabeled compound (+)-**9**, except for the integrated peak area corresponding to the aldehyde signal at δ 9.55. The deuterium content was determined to be 78 ± 1% by ^{1}H NMR.

[14-^{2}H$_1$]-(−)-Modhephen-14-ethylenedithioacetal (10-*d*). Compound (+)-**9**-*d* (210 mg, 0.96 mmol) was sulfur acetalized with 1,2-ethanedithiol (0.25 mL, 0.3 g, 3.19 mmol) and anhydrous $CuSO_4$ (260 mg, 1.60 mmol) by the same procedure used in the preparation of (−)-**10** to give (−)-**10**-*d* (181 mg, 64%) as a clear oil. The title compound showed an identical ^{1}H NMR spectrum to the unlabeled compound (−)-**10**, except for the integrated peak area corresponding to the methine-14 signal at δ 4.77. The deuterium content was determined to be 79 ± 1% by ^{1}H NMR.

[14-^{2}H$_1$]-(−)-Modhephene (1-*d*). Compound (−)-**10**-*d* (355 mg, 1.2 mmol) was desulfurized with Raney nickel (4.3 g) by the same procedure used in the preparation of (−)-**1** to afford (−)-**1**-*d* (186 mg, 75%) as a clear oil. The title compound exhibited identical ^{1}H NMR spectrum to the unlabeled compound (−)-**1**, except for the integrated peak area of the methyl-14 signal at which deuterium was introduced. The deuterium content was estimated to be 76% by ^{1}H NMR.

(+)-Hemiphthalate (12).[7b] Recrystallized from MeOH, mp 102−104 °C; $[\alpha]_{589}$ +6, (*c* 1.13, $CHCl_3$), $[\alpha]^{20}_{578}$ +5, $[\alpha]^{20}_{546}$ +7, $[\alpha]^{20}_{436}$ +11, $[\alpha]^{20}_{365}$ +10; UV (EtOH, ϵ) λ_{max} 225 (7800), 275 (1000); IR ν_{max} ($CHCl_3$) 3508, 1720, 1701, 1600, 1580, 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (br, 1H, COOH), 7.89 (dd, 1H, *J* = 7.4, 1.5 Hz, H3′), 7.68 (dd, 1H, *J* = 7.4, 1.4 Hz, H6′), 7.59 (td, 1H, *J* = 7.3, 1.5 Hz, H5′), 7.56 (td, 1H, *J* = 7.3, 1.5 Hz, H4′), 4.78 (q, *J* = 1.4 Hz, 1H, H3), 4.22 (d, *J* = 10.8 Hz, 1H, pro-*R* H14), 4.08 (d, *J* = 10.8 Hz, 1H, pro-*S* H14), 2.02 (m, 1H, H11), 2.02−1.00 (m, 10H, 5 × CH_2), 1.59 (d, *J* = 1.4 Hz, 3H, H12), 1.04 (s, 3H, H13), 0.92 (d, *J* = 6.5 Hz, 3H, H15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (COOH), 168.1 (COOR), 144.9 (C2), 133.3 (C1′), 132.0 (C5′), 130.8 (C4′), 130.4 (C2′), 129.9 (C3′), 129.4 (C3), 128.8 (C6′), 73.4 (C1), 73.3 (C14), 65.3 (C5), 49.5 (C4), 43.3 (C8), 38.9 (C11), 35.0 (C6), 34.9 (C9), 34.1 (C7), 26.8 (C10), 21.1 (C13), 15.2 (C15), 13.9 (C12). EIMS (20 eV) *m*/*z*: 368 (M^+, 0.1), 190 (19.4), 189 (100).

[14-^{2}H$_1$]-(+)-Hemiphthalate (12-*d*). Compound (−)-**8**-***d*** (140 mg, 0.63 mmol) was esterified with phthalyc anhydride (240 mg, 1.60 mmol) by the same procedure used in the preparation of (+)-**12**[7b] to give (+)-**12**-***d*** (322 mg, 80%) as colorless needles that were recrystallized from MeOH, mp 102−104 °C. The title compound exhibited an identical ^{1}H NMR spectrum to that of hemiphthalate (+)-**12**, except for the integrated peak area corresponding to the ester methylene signals at δ 4.22 and δ 4.08. The deuterium content was determined to be 91 ± 1% by ^{1}H NMR.

(−)-Triquinane 5. Method A. A solution containing (−)-**1** (120 mg, 0.59 mmol) and *p*-TsOH (110 mg, 0.58 mmol) in anhydrous benzene (5 mL) was refluxed for 30 min. The mixture was cooled to room temperature and one aliquot of 1 mL was removed, quenched with saturated aqueous $NaHCO_3$ (3 mL), and extracted with pentane (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give an oily residue (20 mg). The product was an equimolar mixture of (−)-isocomene **3** and (−)-triquinane **5**, as evidenced by ^{1}H NMR analysis. The remaining reaction mixture was refluxed for an additional 1 h and quenched with saturated aqueous $NaHCO_3$ (3 mL). The same workup procedure gave a crude product, which was purified by chromatography on $AgNO_3$-impregnated silica gel (20%, w/w), using hexane as the eluent to afford (−)-**5** (60 mg, 63%) as a clear oil, whose spectral data were identical to those of literature.[6] **Method B.** A solution containing (−)-**3** (24 mg, 0.12 mmol) and *p*-TsOH (27 mg, 0.14 mmol) in 5 mL of anhydrous benzene was refluxed for 90 min. Following the same workup procedure described in method A, the obtained crude product was purified by chromatography on $AgNO_3$-impregnated silica gel (20%, w/w), using hexane as the eluent to afford (−)-**5** (8 mg, 33%) as a clear oil.

[14-^{2}H$_1$]-(−)-Triquinane 5-*d*. A solution containing (−)-**1**-*d* (75 mg, 0.37 mmol) and *p*-TsOH (81 mg, 0.42 mmol) in 3 mL of anhydrous benzene was refluxed for 90 min. The mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ (3 mL). Following the same workup procedure described in method A, the obtained crude product was purified by chromatography on $AgNO_3$-impregnated silica gel (20%, w/w), using hexane as the eluent to afford (−)-**5**-*d* (30 mg, 40%) as a clear oil. The title compound exhibited identical ^{1}H NMR spectrum to the unlabeled compound (−)-**5**, except for the integrated peak area corresponding to the singlet at δ 1.01 assigned to Me14. The deuterium content was determined to be 50 ± 1% by ^{1}H NMR.

Acknowledgment. This research was supported by grants from CONACYT (México). We are grateful to Dr. L. U. Román, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Morelia, México, who kindly supplied an authentic sample of (−)-isocomene.

Supporting Information Available: Copies of ^{1}H NMR spectra of (−)-**1**, (−)-**1**-*d*, (−)-**3**, (−)-**8**-*d*, (+)-**9**, (+)-**9**-*d*, (−)-**10**, (−)-**10**-*d*, **11**, **11**-*d*, (+)-**12**, and (+)-**12**-*d*; ^{13}C NMR spectra of (+)-**9**, and (−)-**10**; EIMS spectra of (−)-**1** and (−)-**1**-*d*; and Cartesian coordinates of calculated minimum energies of (−)-**1**, (−)-**3**, (−)-**5**, (+)-**9**, (+)-**12**, and cations **13**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060258T