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Journal of Molecular Structure 783 (2006) 157–160
Journal of MOLECULAR STRUCTURE
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# Configuration assignment of stereogenic centers in a β-pinene derivative by $^1$H NMR and molecular modeling

Kátia S.P. Perry [a], Jorge L.O. Domingos [b], Ayres G. Dias [c], Sergio Pinheiro [d], Antonio J.R. da Silva [a], Paulo R.R. Costa [b,*]

[a] *Laboratório de Ressonância Magnética Nuclear,Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, bloco H, Ilha da Cidade Universitária, Universidade Federal do Rio de Janeiro, 21941-590, Rio de Janeiro, RJ, Brasil*
[b] *Laboratório de Química Bioorgânica (LQB), Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, bloco H, Ilha da Cidade Universitária, Universidade Federal do Rio de Janeiro, 21941-590, Rio de Janeiro, RJ, Brasil*
[c] *Instituto de Química, Universidade do Estado do Rio de Janeiro, RJ, Brasil*
[d] *Instituto de Química, Universidade Federal Fluminense, RJ, Brasil*

Received 20 June 2005; revised 1 September 2005; accepted 6 September 2005
Available online 17 October 2005

**Abstract**

The absolute configuration of three contiguous newly generated stereocenters in (1*R*,2*R*,3*S*,5*S*,1′*R*)-3-(1′-(4-methoxyphenyl)ethyl)-6,6-dimethylbicyclo [3.1.1] heptan-2-ol (6), stereoselectively prepared from β-pinene in four steps, was established on the basis of $^1$H NMR data and molecular modeling.


*Keywords:* β-Pinene; Configuration assignment; $^1$H NMR; Molecular Modeling; NOE

## 1. Introduction

Naturally occurring α- and β-pinene have been explored as chiral building-blocks in the total synthesis of biologically active compounds [1] and their derivatives have met great success in asymmetric synthesis [2] being employed as chiral auxiliaries [3], reagents [4] and ligands [5]. We have previously reported the use of the (-)-β-pinene derivative **3** (Scheme 1) as a chiral auxiliary in asymmetric Friedel–Crafts reaction (up to 84% d.e.) [6] and in the reduction of β-keto esters (up to 40% d.e.) [7]. This auxiliary was stereoselectively prepared from enone **2**, through hydrogenation of the carbon–carbon double bond followed by reduction of the carbonyl group in the resulting ketone by $LiAlH_4$. Both reactions occurred with total stereoselectivity, being the hydrogen atoms delivered at the opposite side of the methyl group (C8) at the β-pinene moiety (less hindered side). The stereochemistry at C2 and C3 was established by NOE measurements [8].

As part of a program aiming the stereoselective synthesis of new β-pinene derivatives, we decided to prepare alcohols type **3** bearing alkyl groups at the benzylic position, since data obtained by molecular modeling (vide *infra*) suggested that the presence of these groups would impose conformational constraints for the rotation of C–C benzylic bond. The enone **2** was used as starting material for this purpose and the methyl group was chosen to check this assumption.

## 2. Results and discussion

The conjugate addition of dimethyl cuprate to **2** led to ketone **5**, being the two newly generated stereogenic centers, at the benzylic carbon (C1′) and C3, formed with total stereoselectivity, Scheme 2. A possible explanation for the observed stereoselection is to assume the attack of the methyl group taking place at the less hindered face of the carbon–carbon double bond in **2**, leading to the lithium enolate intermediate **4**, having a *R* configuration at C1′. The second stereogenic center at C3 is formed as the protonation of **4** occurs, during the work-up, the proton being delivered at the opposite side of the methyl group C8, leading to the ketone **5**. Similarly, [8] the reduction of the carbonyl group in **5** is stereocontrolled by C8 methyl group and the substituent at C3, leading to alcohol **6**, Scheme 2.

* Corresponding author. Tel.: +55 2125626793; fax: +55 2125626512.
*E-mail address:* lqb@nppn.ufrj.br (P.R.R. Costa).

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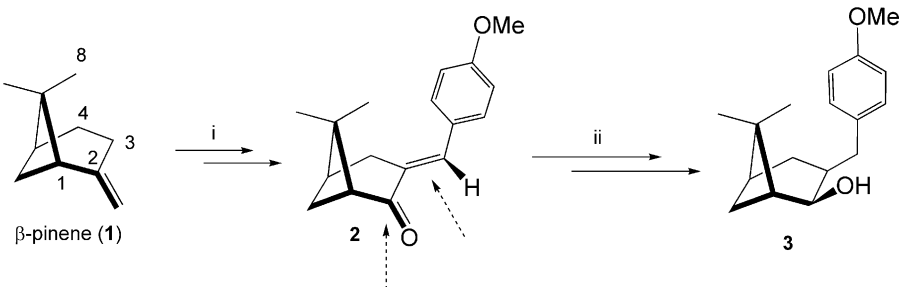
doi:10.1016/j.molstruc.2005.09.001

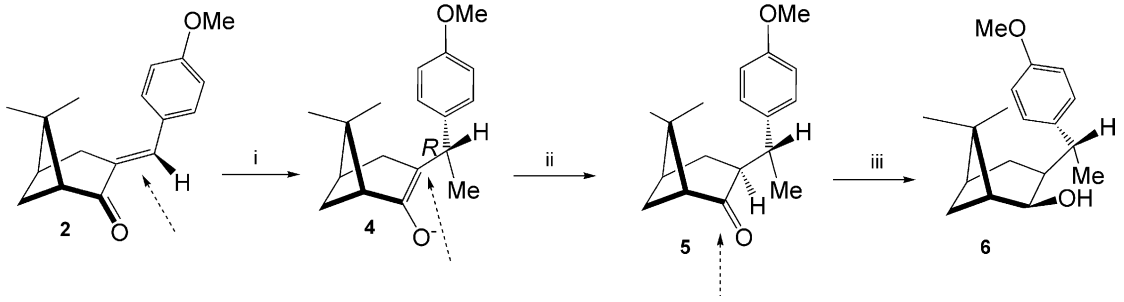



Scheme 1. Stereoselective synthesis of the alcohol **3** from β-pinene. Conditions: (i) and (ii)—Ref. [8].

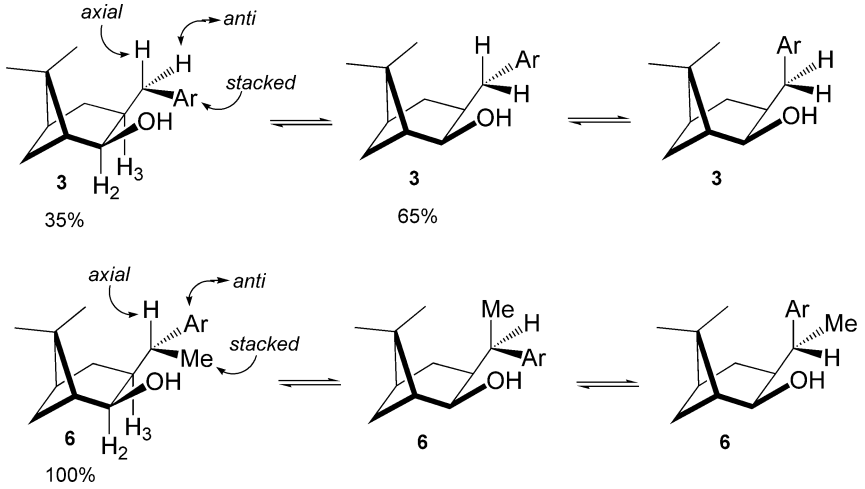
In order to know more about the conformational behavior of alcohols **3** and **6**, we have accomplished a theoretical study (Scheme 3) using molecular mechanics and ab initio calculations (Section 3.1) The results obtained clearly show that the bicycle system is relatively rigid and the conformational freedom of the alicyclic part of the molecule is controlled mainly by steric interactions with C8 methyl group. Only the small hydrogen atom is tolerated at the axial position, near to C8 [9]. Thus, for **3**, two conformers emerged from the calculations, the less populated one having the aryl group in a stacked position while in the more populated one, the aryl group occupies the anti position, less sterically hindered. The comparison of these data with those obtained for **6** shows that the methyl group at the benzylic position imposes severe conformational constraints to the structure and one conformer, in which the hydrogen is placed at the more hindered axial position, has the major population contribution to the conformational equilibrium. These findings suggested that alcohol **6** has low conformational mobility stimulating us to use NOE measurements in order to determine the configuration at the benzylic carbon, as well as at C2 and C3.

The structure of the alcohol **3** was previously studied through NOE experiments [8]. Attempts to determine the relationship between the benzylic hydrogens and H3 through the measurement of the coupling constant failed due to signal overlap.

In the case of **6**, NOE experiments also strongly supported the proposed structure. Irradiation at H2 led to an enhancement of 18% at H3, confirming the *cis*-relationship between these hydrogen atoms (Fig. 1) while the axial position for H1′ was suggested by the 2% increment observed at this hydrogen after




Scheme 2. Stereoselective synthesis of the alcohol **6** from enone **2**. Conditions: (i) $Me_2CuLi$, $Et_2O$, −78 °C to rt; (ii) $NH_4Cl$, 83%; (iii) $LiAlH_4$, THF, 95%.




Scheme 3. Conformational analysis of the alcohols **3** and **6**.

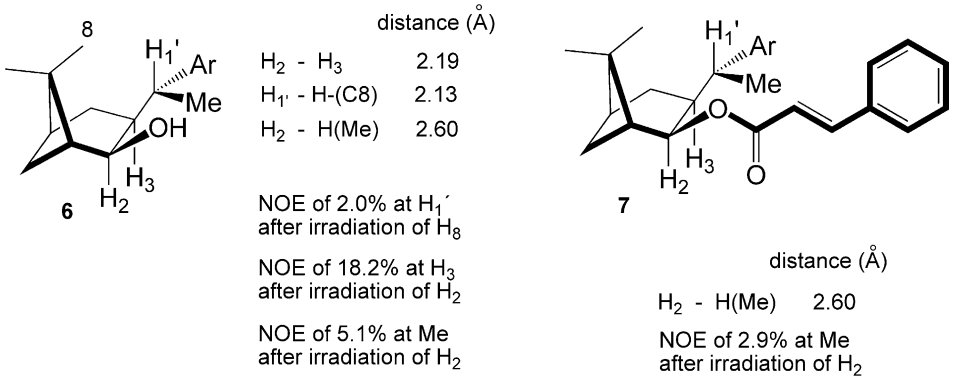



Fig. 1. NOE in alcohol **6** and in the corresponding cinammate **7**. The distances between hydrogens were estimated by molecular modeling.

irradiating the C8 methyl group signal. Finally, the stacked position of the methyl group at the benzylic position was supported by an enhancement of 5.1% observed when H2 is irradiated. These data are in good agreement with the calculated distances between these hydrogen atoms. However, since in **6** the signal for C1′ methyl group overlaps with three other signals, this alcohol was transformed into the corresponding cinnamate **7**. In this derivative, the overlap was removed and the configuration at the benzylic carbon could be confirmed by the observed enhancement at H2 (2.9%) when the Me group was irradiated. In both compounds **6** and **7,** the vicinal coupling constant value for hydrogens H3 and H1′ is 11.4 Hz, which is in full agreement with an anti configuration for the two hydrogens.

In conclusion, the stereogenic centers in alcohol **6**, prepared in two steps from enone **2**, could be assigned through NOE experiments and coupling constant measurements. This structure is in agreement with the expected stereochemical outcome of the reactions and the conformational analysis obtained by molecular modeling calculations.

## 3. Experimental

### 3.1. Computational procedures

#### 3.1.1. Molecular modeling studies

The molecules were constructed using the graphical interface of the Spartan Pro v.1.0 package. They were optimised at the molecular mechanics level using the MMFF force field. The optimised geometries were submitted to a Monte Carlo conformational search at the same level, with 500 steps. The different conformations obtained, differing from the most stable one by no more than 3 kcal $mol^{-1}$, were fully optimised at the MM/MMFF level. Their energies were calculated through single-point calculations at the ab initio HF/6-31G* level. Relative populations for each set of conformers (Scheme 3) were estimated using the Boltzmann distribution law.

### 3.2. NMR experiments

NMR spectra were recorded on a Varian Gemini-200 spectrometer operating at 200 MHz for $^{1}H$ and at 50 MHz for $^{13}C$. Steady-state NOE difference experiments were performed using standard Varian software (NOEDIFF). 1% deuterated chloroform solutions (degassed by freeze–thaw cycles) at 298 K were used for the measurements. A pre-saturation time of 4 s was used and the free induction decays were processed with a line broadening of 2 Hz to minimize artifacts during subtraction.

### 3.3. Synthesis

#### 3.3.1. Materials and methods

The reactions were performed under $N_2$ atmosphere in flame dried glassware. THF and $Et_2O$ were distilled from sodium–benzophenone under $N_2$. $LiAlH_4$, $CuBr.Me_2S$, methyllithium (1.4 M solution in $Et_2O$) and *n*-butyllithium (2.5 M solution in hexanes) were commercially available (Aldrich, Fluka or Merck) and were used as purchased. The compounds **2** and **3** were prepared as described in Ref. [3c].

(1) (1*R*,3*S*,5*S*,1′*R*)-3-(1′-(4-methoxyphenyl)ethyl)-6,6-dimethylbicyclo [3.1.1] heptan-2-one (**5**):

A solution of methyllithium (1.00 mmol) was added in a suspension of $CuBr{\cdot}Me_2S$ (0.29 g—1.14 mmol) in dry diethyl ether (3 mL), under $N_2$ and cooled at 0 °C. The resulting mixture is stirred and cooled at −78 °C, and then a solution of (*E*,1*R*,5*S*)-3-(4-methoxybenzylidene)-6,6-dimethylbicyclo [3.1.1] heptan-2-one (**2**) (0.30 g—1.17 mmol) in $Et_2O$ (1.20 mL) was added. After stirring for 1 h, a solution of $NH_4Cl$ (10 mL) was added, and the resulting mixture was extracted with $CH_2Cl_2$ (3×10 mL). The organic layers were dried with anhydrous $Na_2SO_4$, and the solvent was removed in vacuo. The ketone **5** was obtained in 83% of yield (0.26 g) after purification by flash chromatography (eluent—EtOAc-hexane: 5:95). $^{1}H$ NMR, $CDCl_3$: 7.30–6.70 (m, 4H), 3.80 (s, 3H), 3.39 (q, $J=6.9$ Hz, 1H), 2.80 (m, 1H), 2.53 (t, $J=5.3$ Hz, 1H), 2.44–2.30 (m, 1H), 2.18–2.08 (m, 1H), 1.95 (ddd, $J=13.3$ Hz; 10.2 Hz; 4.7 Hz, 1H), 1.71 (d, $J=10.7$ Hz, 1H), 1.50–1.38 (m, 4H), 1.20 (s, 3H), 0.35 (s, 1H)

(2) (1*R*,2*R*,3*S*,5*S*,1′*R*)-3-(1′-(4-methoxyphenyl)ethyl)-6,6-dimethylbicyclo [3.1.1] heptan-2-ol (**6**):

To a solution of the ketone **5** (0.25 g—0.92 mmol) in THF (4.60 mL) at 0 °C, $LiAlH_4$ (0.06 g—1.56 mmol) was added

and the resulting mixture was stirred during 2.5 h at room temperature. Then, after cooling the mixture to 0 °C, 0.30 mL of an aqueous solution of NaOH (10%) and 0.50 mL of water were added (a vigorous release of $H_2$ was observed). The material was filtered through a Celite pad, and the solvent was removed to stereoselectively obtain the alcohol **6** in 95% of yield (0.24 g). $^1$H NMR, $CDCl_3$: 7.20–6.75 (m, 4H), 4.56–4.44 (m, 1H), 3.80 (s, 3H), 2.86 (dq, $J$ = 11.4 Hz; 6.5 Hz, 1H), 2.32–2.20 (m, 2H), 2.18–2.02 (m, 1H), 1.86–1.76 (m, 1H), 1.40–1.26 (m, 5H), 1.20 (s, 3H), 1.06 (s, 3H); $^{13}$C NMR, $CDCl_3$: 157.34, 138.70, 128.19, 127.99, 113.27, 73.07, 54.85, 47.82, 40.72, 39.94, 39.17, 38.07, 30.48, 27.33, 24.69, 22.66, 21.82

(3) (1*R*,2*R*,3*S*,5*S*,1′*R*)-3-(1′-(4-methoxyphenyl)ethyl)-6, 6-dimethylbicyclo [3.1.1] heptan-2-yl cinnamate (**7**):

To a stirred solution of 6 (0.20 g—0.73 mmol) in THF (1.50 mL) at 0 °C, was added a solution of *n*-BuLi (0.35 mL—0.87 mmol). After 30 min, ethyl cinnamate (0.64 mg—3.65 mmol) dissolved in THF (1 mL) was added and the resulting mixture was stirred for 2 days. The solvent was removed in vacuo and the product was purified by flash chromatography (eluent—EtOAc-hexane: 5:95), to furnish 0.22 g of the cinnamate **7** (75% of yield).$^1$H NMR, $CDCl_3$: 7.73 (d, $J$ = 16.0 Hz, 1H), 7.60–6.80 (m, 9H), 6.49 (d, $J$ = 16.0 Hz, 1H), 5.68 (dd, $J$ = 7.6 Hz; 5.3 Hz, 1H), 3.80 (s, 3H), 2.89 (dq, $J$ = 11.4 Hz; 6.5 Hz, 1H), 2.57–2.38 (m, 2H), 2.21–2.10 (m, 1H), 1.91–1.83 (m, 1H), 1.50–1.44 (m, 3H), 1.19–1.16 (m, 6H), 1.07 (s, 3H); $^{13}$C NMR, $CDCl_3$: 166.30, 157.71, 144.40, 138.31, 134.36, 130.13, 128.75–127.99, 118.63, 113.51, 72.53, 55.08, 45.09, 40.66, 40.06, 38.35, 37.87, 30.37, 27.21, 24.69, 23.00, 21.28

## Acknowledgements

To FINEP-PADCT, CNPq and FUJB for financial support. To Francisco A. Santos for $^1$H NMR and $^{13}$C NMR spectra. To CNPq for financial support and fellowships to the authors.

## References

[1] Somerecent examples G. Mehta, M.K. Bera, Tetrahedron Lett. 45 (2004) 1113; A.R. Hergueta, C. López, F. Fernández, O. Caamaño, J.M. Blanco, Tetrahedron: Asymmetry 14 (2003) 3773; L. Cointeaux, J.-F. Berrien, J. Mahuteau, M.E. Trân Huu-Dâu, L. Cicéron, M. Danis, J. Bioorg. Med. Chem. 11 (2003) 3791.

[2] V. Farina, G.P. Roth, Chem. Today 17 (1999) 39; D.S. Matterson, Chem. Rev. 89 (1989) 1535.

[3] S. Pinheiro, S.F. Pedraza, M.A. Peralta, R.C. Teixeira, F.M.C. Farias, V.F. Ferreira, Tetrahedron: Asymmetry 13 (2002) 2513; S. Pinheiro, C.B.S.S. Gonçalves, M.B. Lima, F.M.C. Farias, Tetrahedron: Asymmetry 11 (2000) 3495; Y. Matsukawa, J.S.D. Kumar, Y. Yoneyama, T. Katagiri, K. Uneyama, Tetrahedron: Asymmetry 11 (2000) 4521; A. Solladié-Cavallo, B. Crescenzi, Synlett (2000) 327.

[4] P.V. Ramachandran, B. Prabhudas, J.S. Chandra, M.V.R. Reddy, H.C. Brown, Tetrahedron Lett. 45 (2004) 1011; P.V. Ramachandran, S. Pitre, H.C. Brown, J. Org. Chem. 67 (2002) 5315; H.C. Brown, D. Murali, B. Singaram, J. Organomet. Chem. 581 (1999) 116; U.P. Dhokte, H.C. Brown, Tetrahedron Lett. 37 (1996) 9021; H.C. Brown, P.V. Ramachandran, J. Organomet. Chem. 500 (1995) 1.

[5] C. Bolm, J.-C. Frison, J. Le Paih, C. Moessner, Tetrahedron Lett. 45 (2004) 5019; G. Chelucci, G. Orrù, G.A. Pinna, Tetrahedron 59 (2003) 9471; G. Chelucci, G. Murineddu, G.A. Pinna, Tetrahedron: Asymmetry 15 (2004) 1373; S.V. Malhotra, Tetrahedron: Asymmetry 14 (2003) 645.

[6] P.R.R. Costa, L.M. Cabral, K.G. Alencar, L.L. Schmidt, M.L.A.A. Vasconcellos, Tetrahedron Lett. 38 (1997) 7021.

[7] K.G. Alencar, U.F. Lima Filho, M.L.A.A. Vasconcellos, P.R.R. Costa, Synth. Commun. 30 (2000) 455.

[8] F. Dumas, K. Alencar, J. Mahuteau, M.J.L. Barbero, C. Miet, F. Gérard, et al., Tetrahedron: Asymmetry 8 (1997) 579.

[9] W. Oppolzer, M. Kurth, D. Reichlein, C. Chapuis, M. Monhaup, F. Moffatt, Helv. Chim. Acta 64 (1981) 2802.