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Configurations of alcohols obtained from dihydro-*O*-acetylisophoto-α-santonic lactone

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Abstract—The configurations of the hydroxyl groups of the reduction products of the ketonic group of *O*-acetylisophoto-α-santonic lactone have been determined by spectroscopy and chemical methods and should be revised to the α and β configurations, for the minor and major alcohol, respectively. The mesylate of the β alcohol yielded readily the disubstituted olefin.

1. Introduction

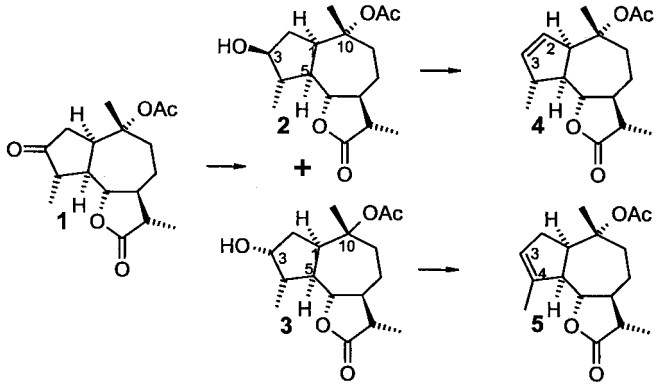
Dihydro-*O*-acetylisophoto-α-santonic lactone **1** and derivatives[1] are a basic reference in the study of guaianolide compounds. The reduction of the ketonic group of this compound with $NaBH_4$ gave two alcohols, **2** and **3**, as shown in Scheme 1, in a 4:1 ratio, whose configurations were assigned erroneously[2] (opposite to those shown in Scheme 1). The Horeau method,[3] which requires pure compounds above all uncontaminated with their epimers, was employed.

On the other hand, the sesquiterpene lactones isolated from the plant *Amberboa lippii*[4] were related[5] to the major alcohol, **2**, and the configuration of the hydroxyl group was established as β (as shown in Scheme 1). Besides, this alcohol has been employed[6] in the synthesis of guaianolide compounds and, significantly, the formation of the double bond at C^3–C^4 could not always be achieved.[6a–c]

Because of the above contrary results and the failed reactions described, the configurations of the hydroxyl groups have been reinvestigated, and on the basis of the spectroscopic and chemical data presented in this paper, it has been found that the configurations should be reversed to β and α for the hydroxyl group of the major compound **2** and the minor compound **3**, respectively.

2. Results and discussion

The minor product **3** was obtained[5] from the reaction mixture by successive chromatographies over silica gel, eluting with hexane–ethyl acetate mixtures and monitoring the purity of the fractions by ^1H NMR. Alternatively, it was synthesized upon treatment of the mesylate of the major product **2** with tetraethylammonium formate followed by hydrolysis of the afforded formate with K_2CO_3 in a 3:1 methanol–water mixture.



Scheme 1.

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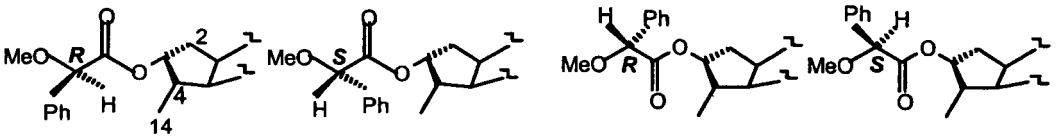

Scheme 2.

Table 1. ^{1}H NMR data of the (*R*)- and (*S*)-MPA esters of the α and β alcohols

Ester	Alcohol α				Alcohol β			
	H_α-2	H_β-2	H-4	H_3-14	H_α-2	H_β-2	H-4	H_3-14
R	1.88	1.96	2.05	0.75	1.13	2.33	2.41	1.04
S	1.62	1.80	2.15	1.08	1.60	2.36	2.20	0.95

Chemical shifts in parts per million (δ) downfield from tetramethylsilane.

The NOESY spectra showed cross peaks for the geminal hydrogen of the hydroxyl group of **2** and **3** and the hydrogens H_2-2, H-4 and H_3-14, but, significantly, n.O.e.s were observed only between H_α-3 and H-1 and H-5 of the alcohol **2**. Besides, the observed coupling or width of the H-3 signals agreed with these configurations: 21 Hz for H_α-3 of **2** and 9 Hz for H_β-3 of **3**. The calculated values were, respectively, 25.50 and 9.90 Hz, obtained with the PC Model program, PCM 4. Thus, the β alcohol is produced mainly because, besides the influence of the heptyl ring with its substituents, the methyl group at C-4 of **1**, although having an α configuration, would be quasi equatorial, and therefore $NaBH_4$ attacks the less hindered α face[7] of the molecule preferentially. For the same reason, *m*-chloroperbenzoic acid produced the α epoxide in the synthesis of (−)-estafiatin.[6c]

These assignments of the hydroxyl groups were confirmed by comparison[8,9] of the chemical shifts of the signals for the protons H_2-2, H-4 and H_3-14 in the spectra of the esters of the (*R*)- and (*S*)-(α-methoxy)phenylacetic (MPA) acids of the two alcohols.

Thus, the signals for the protons H-4 and H_3-14 of the (*R*) ester of the α minor alcohol, Scheme 2 and Table 1, are shifted upfield, due to the aryl ring, relative to the signal for the same protons of the (*S*) ester and, vice versa, the protons H_α-2 and H_β-2 of the (*R*) ester are shifted downfield relative to the equivalent protons of the (*S*) ester. The reverse is applied to the esters of β major alcohol (Scheme 2 and Table 1).

The relative populations of the *sp* conformers (that have the C_α–OMe and C=O bonds *syn* periplanar) with respect to the *ap* conformers (C_α–OMe and C=O bonds *anti* periplanar) of the esters of the (*R*)- and (*S*)-MPA acids are greater at low temperature than at room temperature.[10] When the temperature is decreased, an upfield shift must be observed in the NMR signals of the protons under the shielding cone of the phenyl ring and a downfield shift of the signals of the non-shielded protons of the alcohol. However, the configurations of the hydroxyl groups of the alcohols **2** and **3** could not be assigned unambiguously by comparing the ^{1}H NMR spectra at room temperature and low temperature of a single ester of (*R*)- or (*S*)-MPA of one of the alcohols,[11] probably because these esters have an acetate group at C-10, a lactonic group and a cycloheptane that can affect the chemical shifts of the hydrogens H_2-2, H-4 and H_3-14, and their conformations also depend on temperature as well as the acid part of the esters.[12]

The syntheses of the olefins **4** and **5** also confirm the configurations of the alcohols established herein. The C^2–C^3 double bond of **4**[13] was obtained[2] by heating in pyridine the mesylate of alcohol **2**, readily formed at room temperature, while the minor product **3** did not react at room temperature with mesyl chloride in pyridine because the hydroxyl group was more hindered in **3** than in **2**. Chlorides and decomposition products were formed when the reaction mixture was heated,[2] but this was circumvented by boiling the alcohol **3** in pyridine with mesyl anhydride, affording the olefin **5**.[14]

3. Conclusions

The present results indicate that the formerly reported configuration is erroneous and thus that of the hydroxyl group of the major alcohol obtained by reduction of the ketonic group of dihydro-*O*-acetylisophoto-α-santonic lactone should be revised from α to β.

4. Experimental

4.1. General procedures

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AC 200 or Bruker AMX-500 spectrometers. Chemical shifts are given in parts per million (ppm, δ) downfield from tetramethylsilane (δ_H=0 ppm) and using the centre line of the residual isotopic solvent ($CDCl_3$, δ_C=77.0 ppm) as internal reference. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer. Mass spectra were recorded using a Micromass Autospec instrument. Elemental combustion analyses were performed in a Fisons EA 1108 CHN instrument. Melting points were measured on a Mettler FP 82 hot stage apparatus and are uncorrected. Flash chromatography was performed on Merck Kieselgel (0.063–0.2 mm). Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualized with ultraviolet light, vanillin or oleum solutions as appropriate. Solvents were purified before use according to standard procedures.[15]

4.2. Physical constants of alcohols 2 and 3

The alcohols **2** and **3** were obtained from the ketonic compound **1** by reduction with $NaBH_4$.[2]

4.2.1. 3β-Tetrahydro-*O*-acetyl-isophotosantonic lactone, 2. Mp 104–105°C (ethyl acetate–*n*-hexane), $[\alpha]_D=-25$ (c=0.88 in chloroform); ν_{max} ($CHCl_3$) 3650, 3500 (O–H), 1770 (C=O lactone), 1730 (C=O acetate), 1230 (C–O–C), 1460, 1370, 980 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 4.24 (1H, dd, J=10, 10 Hz, H-6), 3.75 (1H, ddd, $J_{2\alpha,3}$=7, $J_{2\beta,3}$=7, $J_{3,4}$=7 Hz, H-3), 2.93 (1H, ddd, J=9, 9, 9 Hz, H-1), 2.10 and 2.30 (1H each, m, H_2-9), 2.21 (1H, m, H-11), 2.19 (1H, m, H_α-2), 1.98 (3H, s, CH_3–CO–O–), 1.95 (1H, m, H-4), 1.40 and 1.90 (1H each, m, H_2-8), 1.85 (1H, m, H-7), 1.81 (1H, m, H-5), 1.58 (1H, m, H_β-2),1.47 (3H, s, CH_3–C^{10}), 1.21 (3H, d, J=7 Hz, CH_3–C^{11}),1.12 (3H, d, J=7 Hz, CH_3–C^4); δ_C (125 MHz, $CDCl_3$) 178.5 (C=O lactone), 170.2 (–O–*C*O–CH_3), 86.7 (C-10), 84.4 (C-6), 78.0 (C-3), 51.0 (C-5), 49.3 (C-7), 47.0 (C-4), 45.2 (C-1), 42.8 (C-11), 36.0 (C-2), 34.0 (C-9), 25.7 (C-8), 24.6 (*C*H_3–C^{10}), 22.4 (*C*H_3–CO–O–).18.0 (*C*H_3–C^4), 13.1 (*C*H_3–C^{11}). m/z (CI) 311 $[M+H]^+$, 291, 268, 251, 232, 177, 159. Found: $[M+H]^+$, 311.1849; $C_{17}H_{26}O_5$ requires: $[M+H]^+$, 311.1858. Found: C, 65.63; H, 8.80. $C_{17}H_{26}O_5$ requires: C, 65.78; H 8.44%.

4.2.2. 3α-Tetrahydro-*O*-acetyl-isophotosantonic lactone, 3. Mp 82–84°C (ethyl acetate–*n*-hexane), $[\alpha]_D=-54.2$ (c=1.05 in chloroform); ν_{max} ($CHCl_3$) 3590 (O–H), 1760 (C=O lactone), 1710 (C=O acetate), 1240 (C–O–C), 1450, 1360, 980 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 4.16 (1H, ddd, $J_{2\alpha,3}$=2.5, $J_{2\beta,3}$=2.5, $J_{3,4}$=4 Hz, H-3), 4.07 (1H, dd, J=10, 10 Hz, H-6), 3.23 (1H, ddd, J=9, 9, 9 Hz, H-1), 2.20 (1H, m, H-11), 2.20 and 1.76 (1H each, m, H_2-9), 2.13 (1H, ddd, J=9.4, 10, 10 Hz, H-5), 2.01 (1H, m, H-4), 1.97 (3H, s, CH_3–CO–O–), 1.87 (1H, m, H_α-2), 1.87 (1H, m, H_β-2), 1.85 (1H, m, H-7), 1.80 and 1.30 (1H each, m, H_2-8), 1.42 (3H, s, CH_3–C^{10}), 1.22 (3H, d, J=7 Hz, CH_3–C^{11}), 1.16 (3H, d, J=7 Hz, CH_3–C^4); δ_C (125 and 50 MHz, $CDCl_3$) 178.5 (C=O lactone), 170.1 (–O–*C*O–CH_3), 87.1 (C-10), 85.1 (C-6), 74.2 (C-3), 49.9 (C-7), 49.3 (C-5), 46.4 (C-1), 45.1 (C-4), 42.1 (C-11), 36.3 (C-9), 35.7 (C-2), 25.7 (C-8), 23.0 (*C*H_3–C^{10}), 22.4 (*C*H_3–CO–O–). 14.0 (*C*H_3–C^4), 12.8 (*C*H_3–C^{11}). m/z (CI) 311 $[M+H]^+$, 291, 268, 251, 232, 177, 159. Found: $[M+H]^+$, 311.1797; $C_{17}H_{26}O_5$ requires: $[M+H]^+$, 311.1858. Found: C, 65.43; H, 8.73. $C_{17}H_{26}O_5$ requires: C, 65.78; H 8.44%.

The double resonance, ^1H–^1H COSY, HMQC, HMBC, NOESY, ROESY and GOESY experiments of the two alcohols agree with the above assignments.

4.2.3. 3α-Tetrahydro-*O*-acetyl-isophotosantonic lactone, 3 (obtention of alcohol 3 from alcohol 2)[2]. To a solution of alcohol **2** (203 mg) in pyridine (4 ml) was added methanesulfonyl chloride (0.2 ml) and the mixture was left overnight. The reaction mixture was diluted with diethyl ether and the solution was washed with hydrochloric acid (10%), brine and dried ($MgSO_4$). The solution was filtered and the solvent was removed under reduced pressure to give the crude mesylate of **2**. This product in acetone (50 ml) was heated under reflux for 20 h with an excess of tetraethylammonium formate. The solvent was removed under reduced pressure, and the residue rinsed with diethyl ether and dissolved in water. The aqueous solution was washed with diethyl ether, the combined filtrate and washings were washed sequentially with water, saturated aqueous $NaHCO_3$, water, brine and dried ($MgSO_4$). The solution was filtered and the solvent was eliminated under reduced pressure. The residue (215 mg) was chromatographed over preparative (1 mm) layer plates (Merck Kieselgel 60 F_{254}) to give the formate of **3** (147 mg) and the olefin **4**[13] (17 mg).

4.3. Hydrolysis of formate

To a solution of formate (115 mg) in methanol (1.5 ml), a 23% aqueous solution of K_2CO_3 (0.5 ml) was added and the solution was left overnight at room temperature, poured over hydrochloric acid (5%) and extracted with $CHCl_3$. The organic phase was washed sequentially with water, saturated aqueous $NaHCO_3$, water, brine and dried ($MgSO_4$). The solution was filtered and the solvent was removed under reduced pressure. The residue was chromatographed over preparative (1 mm) layer plates (Merck Kieselgel 60 F_{254}) to give the alcohol **3** (94 mg), identical with that obtained from the mixture of the reaction of compound **1** with $NaBH_4$.

4.4. Synthesis of (*R*)- and (*S*)-MPA esters of alcohols 2 and 3

The esters were obtained by method 1 in Ref. 9. For example: to a solution of the alcohol **3** (12.1 mg, 0.038 mmol) in CH_2Cl_2 (1 ml), (*S*)-MPA (12.5 mg, 0.075 mmol), *N*,*N*′-dicyclohexylcarbodiimide (19.3 mg, 0.093 mmol) and 4-(dimethylamino)pyridine (6.9 mg, 0.056 mmol) were consecutively added. The progress of the reaction was monitored by TLC until the total reaction of the alcohol (22 h). The solvent was removed under reduced pressure, and the solid residue was treated with ethyl acetate, eliminating the insoluble solid products by filtration. The organic phase was washed sequentially with hydrochloric acid (10%), saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). The solution was filtered and the solvent was removed under reduced pressure and the residue was purified by chromatotron chromatography over silica gel plate (1 mm), eluting with 80 ml of hexane–ethyl acetate mixtures, starting with hexane–ethyl acetate (95:5, v/v) and increasing the proportion of ethyl acetate in each mixture by a volume of 5%. The ester was obtained with the hexane–ethyl acetate (75:25, v/v) mixture.

4.4.1. 3β-Tetrahydro-*O*-acetyl-isophotosantonic lactone [(*R*)-(α-methoxy)phenylacetate]. (*R*)-MPA ester of alcohol **2**: δ_H (500 MHz, $CDCl_3$), 7.42–7.34 (5H, m, C_6H_5–$CHOCH_3$–CO–), 4.75 (1H, ddd, J=3.8, 7.4, 3.5 Hz, H-3), 4.73 (1H, s, *H*–$COCH_3C_6H_5$–CO–), 3.69 (1H, dd, J=10, 10 Hz, H-6), 3.40 (3H, s, C*H*$_3$–O–CHC_6H_5–CO–), 2.74 (1H, ddd, J=8.5, 8.5, 10.5 Hz, H-1), 2.41 (1H, ddq, J=3.5, 3.5, 7 Hz, H-4), 2.33 (1H, ddd, J=8.5, 15, 7.4 Hz, H_β-2), 2.10 (1H, several overlapping signals, H-11), 1.95 (3H, s, CH_3–CO–O–), 1.80 (1H, several overlapping signals, H-7), 1.70 (1H, several overlapping signals, H-5), 1.37 (3H, s, CH_3–C^{10}), 1.18 (3H, d, J=7 Hz, CH_3–C^{11}),

1.13 (1H, ddd, J=8.5, 15, 3.8 Hz, H_α-2), 1.04 (3H, d, J=7 Hz, CH_3-4).

4.4.2. 3β-Tetrahydro-*O*-acetyl-isophotosantonic lactone [(*S*)-(α-methoxy)phenylacetate]. (*S*)-MPA ester of alcohol **2**: δ_H (500 MHz, $CDCl_3$), 7.42–7.32 (5H, m, C_6H_5–$CHOCH_3$–CO–), 4.74 (1H, s, *H*–$COCH_3C_6H_5$–CO–), 4.71 (1H, ddd, J=6.2, 8.1, 6.9 Hz, H-3), 3.83 (1H, dd, J=10, 10 Hz, H-6), 3.41 (3H, s, CH_3–O–CHC_6H_5–CO–), 2.83 (1H, ddd, J=11.2, 8.6, 11 Hz, H-1), 2.36 (1H, ddd, J=8.6, 13.6, 8.1 Hz, H_β-2), 2.20 (1H, ddq, J=6.9, 4.8, 7 Hz, H-4), 2.09 (1H, m, H-11), 1.98 (3H, s, CH_3–CO–O–), 1.80 (1H, m, H-7), 1.77 (1H, several overlapping signals, H-5), 1.60 (1H, ddd, J=11.2, 13.6, 6.2 Hz, H_α-2), 1.45 (3H, s, CH_3–C^{10}), 1.18 (3H, d, J=7 Hz, CH_3–C^{11}), 0.95 (3H, d, J=7 Hz, CH_3–C^4).

4.4.3. 3α-Tetrahydro-*O*-acetyl-isophotosantonic lactone [(*R*)-(α-methoxy)phenylacetate]. (*R*)-MPA ester of alcohol **3**: δ_H (500 MHz, $CDCl_3$), 7.43–7.32 (5H, m, C_6H_5–$CHOCH_3$–CO–), 5.18 (1H, dd, J=4.2, 4.2 Hz, H-3), 4.73 (1H, s, *H*–$COCH_3C_6H_5$–CO), 3.99 (1H, dd, J=10, 10 Hz, H-6), 3.41 (3H, s, CH_3–O–CHC_6H_5–CO–), 3.22 (1H, ddd, J=9, 9, 9 Hz, H-1), 2.12 (1H, several overlapping signals, H-11), 2.05 (1H, several overlapping signals, H-4), 2.02 (1H, several overlapping signals, H-5), 1.96 (1H, ddd, J=9, 14.6, 4.2 Hz, H_β-2), 1.95 (3H, s, CH_3–CO–O–), 1.88 (1H, dd, J=9, 14.6 Hz, H_α-2), 1.80 (1H, several overlapping signals, H-7), 1.35 (3H, s, CH_3–C^{10}), 1.21 (3H, d, J=7 Hz, CH_3–C^{11}), 0.75 (3H, d, J=6.7 Hz, CH_3–C^4).

4.4.4. 3α-Tetrahydro-*O*-acetyl-isophotosantonic lactone [(*S*)-(α-methoxy)phenylacetate]. (*S*)-MPA ester of alcohol **3**: δ_H (500 MHz, $CDCl_3$), 7.44–7.33 (5H, m, C_6H_5–$CHOCH_3$–CO–), 5.23 (1H, dd, J=4.9, 4.9 Hz, H-3), 4.75 (1H, s, *H*–$COCH_3C_6H_5$–CO–), 4.01 (1H, dd, J=10, 10 Hz, H-6), 3.42 (3H, s, CH_3–O–CHC_6H_5–CO–), 2.88 (1H, ddd, J=8, 9.6, 9.6 Hz, H-1), 2.19 (1H, m, H-11), 2.15 (1H, ddq, J=4.9, 9.7, 7 Hz, H-4), 2.02 (1H, ddd, J=9.6, 9.7, 10 Hz, H-5), 1.92 (3H, s, CH_3–CO–O–). 1.80 (1H, ddd, J=9.6, 15, 4.9 Hz, H_β-2),1.80 (1H, m, H-7), 1.62 (1H, dd, J=8, 15 Hz, H_α-2),1.29 (3H, s, CH_3–C^{10}), 1.22 (3H, d, J=7 Hz, CH_3–C^{11}), 1.08 (3H, d, J=7 Hz, CH_3–C^4).

The double resonance, ^1H–^1H COSY, NOESY, ROESY and GOESY experiments of the four esters agree with the above assignments.

4.4.5. 3,4-Didehydro-3-deoxo-dihydro-*O*-acetyl-isophotosantonic lactone, 5. Olefin **5**. Alcohol **3** (10.1 mg), with an excess of methane sulfonic acid anhydride, in pyridine (1 ml) was heated under reflux in inert atmosphere for 6 h. The reaction mixture was diluted with ethyl acetate and the solution obtained was sequentially washed with water, sulfuric acid (10%), water, saturated aqueous $NaHCO_3$, water and brine, and dried ($MgSO_4$). The solution was filtered and the solvent was eliminated under reduced pressure. The residue (12.7 mg) was purified by flash chromatography over silica gel (column), eluting with hexane–ethyl acetate (70:30, v/v), to afford olefin **5** (2.4 mg), yield 23%. δ_H (500 MHz, $CDCl_3$), 5.46 (1H, s, H-3), 4.12 (1H, dd, J=10, 10 Hz, C_6–H), 3.03 (1H, ddd, J=8, 8, 8 Hz, H-1), 2.63 (1H, dd, J=9, 9 Hz, H-5), 2.30 (1H, m, H_α-9), 2.28 (2H, m, H_2-2), 2.18 (1H,m, H-11), 2.09 (1H, m, H_β-9), 2.06 (1H, m, H-7), 2.03 (3H, s, CH_3–CO–O–), 1.90 and 1.42 (1H each, m, H_2-8), 1.86 (3H, s, CH_3–C^4), 1.46 (3H, s, CH_3–C^{10}), 1.21 (3H, d, J=7 Hz, CH_3–C^{11}).

The double resonance and ^1H–^1H COSY experiments agree with the above assignments.

Acknowledgements

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References

1. Barton, D. H. R.; Levisalles, J. E. D.; Pinhey, J. T. *J. Chem. Soc.* **1962**, 3472–3482.
2. White, E. H.; Eguchi, S.; Marx, J. N. *Tetrahedron* **1969**, *25*, 2099–2115.
3. (a) Horeau, A. *Tetrahedron Lett.* **1961**, *12*, 506–512. (b) Horeau, A. *Tetrahedron Lett.* **1962**, *13*, 965–969. (c) Marquet, A.; Horeau, A. *Bull. Soc. Chim. Fr.* **1967**, 124–128.
4. González, A. G.; García Marrero, B.; Bretón, J. L. *An. Quim.* **1970**, *66*, 799–811.
5. González, A. G.; García Marrero, B. *An. Quím.* **1978**, *74*, 1121–1124.
6. (a) Marx, J. N.; White, E. H. *Tetrahedron* **1969**, *25*, 2117–2120. (b) Marx, J. N.; McGauguey, S. M. *Tetrahedron* **1972**, *28*, 3583–3586. (c) Edgar, M. T.; Greene, A. E.; Crabbé, P. *J. Org. Chem.* **1979**, *44*, 159–160. (d) Bargues, V.; Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *Tetrahedron* **1998**, *54*, 1845–1852.
7. See for example: Battersby, A. R.; Hall, E. S.; Southgate, R. *J. Chem. Soc.* **1969**, 721–728.
8. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
9. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
10. Seco, J. M.; Latypov, Sh.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **1995**, *6*, 107–110.
11. Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877–882.
12. See note 26 in Ref. 8.
13. The ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, HMBC, HMQC and ROESY experiments agree with the structure **4**.
14. The improvement in the yield was not intended and other methods of synthesis were not attempted.
15. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.