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Stereochemical Outcome of Aldol Reaction of a 6-C-Substituted D-Mannose Derivative

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The base-promoted cyclization of the diketose **3** has been studied. The structural assignments of the aldol products **4a**, **4b**, and **4c** were based on the spectroscopic analysis and the chiroptical properties.

As a part of a project aimed at the synthesis of carbocyclic analogs of (−)-swainsonine we were interested in the preparation of the α,β-unsaturated ketone **5a** as a valuable intermediate for the synthesis of several potential enzyme inhibitors. Retrosynthetic analysis of **5a** led to the diketose **3** which would easily make accessible the route to our target molecule by intramolecular aldol condensation.

Results and Discussion

1) Preparation of the Substrate. The ketose **2** was prepared from D-mannose **1** by application of a seven-step sequence with 45% overall yield, following our previously described procedure (Scheme 1).[1] Wacker oxidation[2] of **2** led to the isolation of the diketose **3** (87%) by flash chromatography.

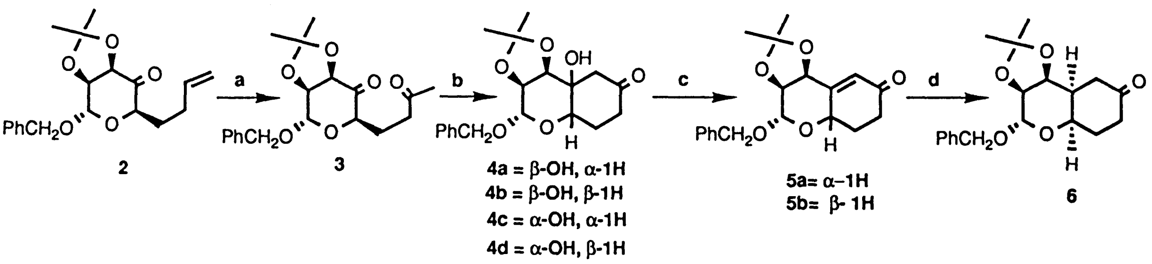
2) Cyclization Reactions. The results obtained in the cyclization of **3** under basic conditions are shown in Table 1. The structural assignments of the aldols **4a**, **4b**, and **4c** were based on the following basis:

a) The chair conformation of the pyran with a β-equatorial 3-H for **4a** and **4c** and a β-axial 3-H for **4b** was confirmed by the appearance of singlets at δ=5.18 (**4a**) and δ=5.14 (**4c**) and a doublet at δ=4.60 (**4b**) in the ^{1}H NMR spectra.

b) The half-height width values obtained in the ^{1}H NMR spectra for the 1-H protons of **4a** ($W_{1/2}$=18 Hz); **4b** ($W_{1/2}$=8 Hz) and **4c** ($W_{1/2}$=9 Hz) allowed us to confirm the trans (**4a**) and the cis (**4b** and **4c**) junction in the decalone system.[3]

c) The chemical shifts obtained for 6-C in the ^{13}C NMR spectra of **4a** (δ=70.56) and **4c** (δ=74.69) allowed us to confirm the axial and the equatorial orientation of the OH group in **4a** and **4c** respectively, in agreement with the data in the literature.[4]

d) The sign of the Cotton effect exhibited by **4a** is in good accordance with the octant rule predictions for t3′ eq decalones.[5] However, the qualitative understanding of the negative Cotton effect exhibited by **4c** ($\Delta\xi_{285}=-0.20$) would only be achieved in terms of the *dissignate* behavior[6] of the β-axial OH of the c3′ eq decalone by comparison with the positive Cotton effect obtained for the *cis* decalone **6** ($\Delta\xi_{292}=+0.14$) (Fig. 1). Likewise, a *dissignate* effect of the OH β-axial substituent in **4b** may account for the positive Cotton effect



a: Wacker, 87%; b: base, Table 1; c: $SOCl_2$, pyr, 0°C,72%; d: H_2, Pd, 97%

Scheme 1.

Table 1.

Entry	Base (equiv)	4a	4b	4c	Time	Temp	Yield	Solvent
1	KOH (1)	43	42	—	20 min	rt	85	CH_3OH
2	KOH (1)	52	35	—	24 h	rt	87	CH_3OH
3	Pyrrolidine (1)	13	—	80	2.5 h	0 °C	93	Ether
4	Pyrrolidine (1)	95	—	—	24 h	rt	95	Ether
5	Piperidine (1)	10	45	45	2.5 h	rt	96	Ether

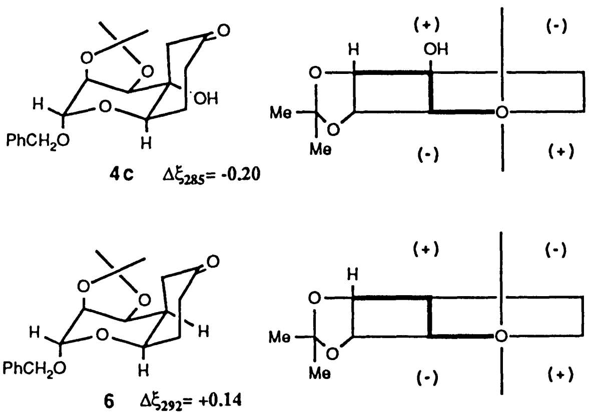


Fig. 1. Perspective drawing and octant projections for **4c** and **6**.

exhibited by the c3′ eq decalone.

3) Stereochemical Outcome of the Cyclization. Treatment of **4a** with either pyrrolidine (1 equiv) or aqueous KOH (1 equiv) at room temperature for 24 h led to the quantitative recovery of the starting material, while reaction of the aldol **4c** and the diketose **3** with pyrrolidine (1 equiv) at room temperature for 24 h led quantitatively to **4a** in both cases. The base-promoted transformation of **4c** into **4a** defines the last compound as being the thermodynamically controlled aldol product with a 1α-H configuration.

The formation of **4c** as the major product under kinetically controlled conditions (Table 1, Entry 3) is in good agreement with the well-known stereoelectronic control of this type of cyclization processes.[7–10]

Treatment of **3** with aqueous KOH (Table 1, Entries 1 and 2) led to a mixture of aldols **4a**:**4b** (1 : 1) while reaction of **3** with piperidine (1 equiv) at room temperature for 2.5 h afforded a mixture of the three aldols **4a** (10%), **4b** (45%) and **4c** (45%). The fact that we have been unable to detect the presence of the *trans* aldol **4d** in our cyclization experiments could be explained by the combination of two additive factors: the steric effect caused by the angular OR group and the stereoelectronic effect associated with the axial attack of the enolate ion to the cyclic ketone.

4) Formation of the α,β-Unsaturated Ketones 5a and 5b. Treatment of the *trans* aldol **4a** and *cis* aldol **4c** with thionyl chloride in pyridine afforded the α,β-unsaturated ketone **5a** with 67% and 72% isolated yields respectively. Analogous treatment of **4b** led to the enone **5b** in 67% isolated yield.

Hydrogenation of **5a** afforded the saturated ketone **6** in 97% yield. Evidence for the *cis*-decalin system in **6** was obtained by ^{1}H NMR experiments.[11]

Conclusions

The base-promoted aldol cyclization of the diketose **3** led to the aldol products **4a** and **4c** under thermodynamic and kinetic controlled conditions, respectively. Structural assignment was based on the conventional spectroscopic analysis and the chiroptical properties. The *dissignate* behavior of the axial OH group (β axial substituent) in **4c** was unequivocally confirmed by the possitive Cotton effect obtained for the *cis* decalone **6**.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a digital Perkin–Elmer 241 polarimeter in a 1-dm cell. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 MHz and 50.3 MHz respectively. The IR spectra were determined on a Beckman 33-IR spectrophotometer as indicated in each case. Mass spectra were recorded on a V.G. TS-250 apparatus. Elemental analyses were carried out using a Perkin–Elmer 240 B Analyser. Optical rotatory dispersion curves were measured on a Jobin-Ybon Dichrograph III.

Benzyl 6,7,9-Trideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-4,8-nonodiulopyranoside (3). Copper(I) chloride (1 g, 10 mmol) and palladium chloride (0.36 g, 2 mmol) were suspended in *N,N*-dimethylformamide (10 ml) and water (1.2 ml). The mixture was shaken under an oxygen atmosphere until the absorption of oxygen had ceased. Then, a solution of the ketose **2** (3.3 g, 10 mmol) in *N,N*-dimethylformamide (2 ml) was added dropwise and the mixture was filtered through a column packed with Celite and washed with ethyl acetate. The organic phase was washed with brine, dried on Na_2SO_4 to give, after evaporation of the solvent, 3.2 g of a residue which was fractionated by flash chromatography on silica gel. Elution with hexane–AcOEt (8 : 2), afforded a yellow oil **3** (3 g, 87%). $[\alpha]_D$ +100.8° (*c* 1.0, $CHCl_3$). Calcd for $C_{19}H_{24}O_6$ (MW 348): C, 65.51; H, 6.89%. Found: C, 65.48; H, 6.93%. ^{1}H NMR ($CDCl_3$) δ=1.32 (s, 3H), 1.45 (s, 3H), 2.05 (m, 2H, 6-H), 2.13 (s, 3H), 2.58 (t, 2H, J=7 Hz, 7-H), 4.22 (dd, 1H, $J_{5,6}$=5 Hz, $J_{5,6'}$=8 Hz, 5-H), 4.42 (AB system, J=7 Hz, 2-H+3-H), 4.61 (AB system, J=12 Hz, $ArCH_2$), 5.02 (s, 1H, 1-H), 7.31 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=24.16 (t), 25.10 (q), 26.39 (q), 29.46 (q), 38.51 (t), 69.76 (t), 72.20 (d), 75.53 (d), 78.40 (d), 95.81 (d), 110.02 (s), 127.88 (d), 128.34 (d), 128.32 (d), 136.11 (s), 203.59 (s), 207.61 (s).

Aldol Reactions. a) Cyclization of 3 with KOH. Aqueous KOH (4%) (4 ml, 3 mmol) was added dropwise to a solution of **3** (1 g, 3 mmol) in methanol (3 ml) at 0 °C. The reaction mixture was stirred at room temperature for 20 min. Evaporation of the methanol at reduced pressure was followed by addition of 2 ml of an aqueous saturated NH_4Cl solution and extraction with ethyl acetate. The combined organic layers were washed with brine, dried on Na_2SO_4 to give, after evaporation of the solvent, 0.9 g of a crude product which was flash chromatographed on silica gel.

(1*R*,3*S*,4*S*,5*R*,6*S*)-3-Benzyloxy-6-hydroxy-4,5-isopropylidenedioxy-2-oxabicyclo[4.4.0]decan-8-one (4a). Elution with hexane–AcOEt (8 : 2) yielded **4a** (0.43 g, 43%); mp 150 °C (acetone). $[\alpha]_D$ +44.8° (*c* 1.3, $CHCl_3$). Calcd for $C_{19}H_{24}O_6$ (MW 348): C, 64.51; H, 6.89%. Found: C, 65.43; H, 6.83%. CD (CH_3OH) $\Delta\xi_{285}$=−1.53. IR (film) ν_{max} 3400, 1725, 1500, 1390, 1220, 1070, 1020, 920, 850, 750 cm^{-1}. ^{1}H NMR ($CHCl_3$) δ=1.34 (s, 3H), 1.54 (s, 3H), 2.0 (m, 2H, 10-H), 2.18 (dd, 1H, J_1=14 Hz, J_2=1.5 Hz, 7α-H), 2.3 (m, 2H, 9-H), 2.69 (dd, 1H, J_1=14 Hz, J_2=2.5 Hz, 7β-H), 4.00 (m, 1H, $W_{1/2}$=18 Hz, 1-H), 4.01 (d, 1H, $J_{4,5}$=6 Hz, 5-H), 4.12 (d, 1H, $J_{4,5}$=6

Hz, 4-H),4.66 (AB system, J=12 Hz, $ArCH_2$), 5.18 (s, 1H, 3-H), 7.35 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=25.36 (q), 25.81 (t), 25.88 (q), 38.70 (t), 48.91 (t), 67.16 (d), 69.87 (t), 70.56 (s), 73.93 (d), 75.91 (d), 96.88 (d), 109.91 (s), 128.04 (d), 128.10 (d), 128.48 (d), 137.02 (s), 206.30 (s). MS (CI) (*m*/*z*, %) 349 (M^++1, 30), 331 (90), 241 (95), 156 (75), 91 (100).

(1*S*,3*S*,4*S*,5*R*,6*S*)-3-Benzyloxy-6-hydroxy-4,5-isopropylidenedioxy-2-oxabicyclo[4.4.0]decan-8-one (4b). Elution with hexane–AcOEt (75 : 25) yielded 0.42 g (42%) of **4b** mp 133—134 °C (ether). $[\alpha]_D$ +153.2° (*c* 1.0, $CHCl_3$). Calcd for $C_{19}H_{24}O_6$ (MW 348): C, 65.51; H, 6.89%. Found: C, 65.42; H, 6.80%. CD (CH_3OH) $\Delta\xi_{285}$=+2.6×10^{-2}. IR (film) ν_{max} 3350, 1720, 1600, 1520, 1050, 880, 750, and 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.34 (s, 6H), 2.20 (m, 2H, 10-H), 2.27 (d, 1H, J=14 Hz, 7α-H), 2.60 (m, 2H, 9-H), 2.80 (dd, 1H, J_1=14 Hz, J_2=1.5 Hz, 7β-H), 3.70 (m, 1H, $W_{1/2}$=8 Hz, 1-H), 3.98 (d, 1H, $J_{4,5}$=5 Hz, 5-H), 4.06 (dd, 1H, $J_{4,5}$=5 Hz, $J_{3,4}$=6 Hz, 4-H), 4.60 (d, 1H, $J_{3,4}$=6 Hz, 3-H), 4.78 (AB system, J=12 Hz, $ArCH_2$), 7.35 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=25.67 (d), 26.07 (q), 27.70 (q), 35.92 (t), 46.99 (t), 70.37 (d), 70.62 (t), 73.97 (s), 76.65 (d), 79.11 (d), 101.37 (d), 110.64 (s), 127.94 (d), 127.96 (d), 128.33 (d), 137.07 (s), 207.49 (s). MS (CI) (*m*/*z*, %) 349 (M^++1, 90), 331 (40), 241 (100), 195 (65), 91 (98).

Treatment of **3** (1 g, 3 mmol) with aqueous KOH (4%) (4.2 ml, 3 mmol) at room temperature for 24 h led to **4a** (52%) and **4b** (35%).

b) Cyclization of 3 with Pyrrolidine. Pyrrolidine (0.25 ml, 3.1 mmol) was added by syringe at 0 °C under nitrogen to a magnetically stirred solution of **3** (1.1 g, 3.1 mmol) in 25 ml of dry ether. After 2.5 h the solvent was evaporated to yield 1.2 g of a crude extract which was flash-chromatographed on silica gel.

(1*R*,3*S*,4*S*,5*R*,6*R*)-3-Benzyloxy-6-hydroxy-4,5-isopropylidenedioxy-2-oxabicyclo[4.4.0]decan-8-one (4c). Elution with hexane–AcOEt (8 : 2) yielded 0.8 g (80%) of a colorless oil **4c**, $[\alpha]_D$ +33.1° (*c* 1.1, $CHCl_3$). Calcd for $C_{19}H_{24}O_6$ (MW 348): C, 65.51; H, 6.89%. Found 65.41; H, 6.80%. CD (CH_3OH) $\Delta\xi_{285}$=−0.20. IR (film) ν_{max} 3400, 1715, 1600, 1380, 1020, 860, 760, 740, and 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.29 (s, 3H), 1.49 (s, 3H), 2.0 (m, 2H, 10-H), 2.25 (m, 1H, 9α-H), 2.40 (d, 1H, J=14 Hz, 7α-H), 2.60 (m, 2H, 9β-H), 2.77 (d, 1H, J=14 Hz, 7β-H), 3.85 (m, 1H, $W_{1/2}$=9 Hz, 1-H), 4.22 (d, 1H, $J_{4,5}$=7 Hz, 5-H), 4.28 (d, 1H, $J_{4,5}$=7 Hz, 4-H), 4.63 (AB system, J=12 Hz, $ArCH_2$), 5.14 (s, 1H, 3-H), 7.32 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=24.85 (q), 25.43 (q), 25.71 (t), 36.11 (t), 46.97 (t), 66.20 (d), 69.43 (t), 74.69 (s), 76.08 (d), 80.00 (d), 97.05 (d), 109.43 (s), 128.03 (d), 128.05 (d), 128.46 (d), 136.93 (s), 209.73 (s). MS (CI) (*m*/*z*, %) 349 (M^++1, 35), 331 (40), 241 (100), 91 (90).

4a: Elution with hexane–AcOEt (75 : 25) yielded **4a** (0.143 g, 13%).

Treatment of **3** (1.1 g, 3.1 mmol) with pyrrolidine (0.25 ml, 3.1 mmol) in ether at room temperature for 24 h yielded **4b** (95%).

c) Cyclization of 3 with Piperidine. To a magnetically stirred solution of **3** (0.95 g, 2.7 mmol) in 20 ml of dry ether at 0 °C was added dropwise piperidine (0.23 ml, 2.7 mmol). After 2.5 h the organic solvent was evaporated to give 0.97 g of residue which was flash-chromatographed on silica gel. Elution with hexane–AcOEt (8 : 2) yielded **4c** (0.37 g, 45%), **4a** (0.09 g, 10%) and **4b** (0.47 g, 45%).

Dehydration Reactions. (1*R*,3*S*,4*S*,5*S*)-3-Benzyloxy-4,5-isopropylidenedioxy-2-oxabicyclo[4.4.0]dec-6-en-8-one (5a from 4a and 4c). Thionyl chloride (0.23 ml, 3.15 mmol) was added dropwise under nitrogen at −10 °C to a solution of **4c** (1 g, 2.87 mmol) in pyridine (0.28 ml, 3.45 mmol). The reaction mixture was stirred overnight at 0 °C. It was then poured into a flask containing 10 ml of an aqueous saturated sodium hydrogencarbonate solution and extracted with dichloromethane (3×10 ml). The combined organic layers were washed with brine and dried on Na_2SO_4. The evaporation of the solvent at reduced pressure yielded a yellow oil **5a** (0.68 g, 72%). $[\alpha]_D$ +16.08° (*c* 1.0, $CHCl_3$). Calcd for $C_{19}H_{22}O_5$ (MW 330): C, 69.09; H, 6.66%. Found: C, 69.15; H, 6.60%. CD (CH_3OH) $\Delta\xi_{325}$=−0.36; $\Delta\xi_{245}$=+2.09; $\Delta\xi_{217}$=−6.2. UV (CH_3OH) λ_{max}=245 (ξ=1.6×10^4) nm. IR (film) ν_{max} 1685, 1500, 1460, 1380, 1230, 1150, 1100, 1080, 1020, 910, 860, 780, 760, 740, and 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.35 (s, 3H), 1.40 (s, 3H), 2.05 (m, 2H, 10-H), 2.4 (m, 2H, 9-H), 4.15 (dd, 1H, $J_{3,4}$=1.5 Hz, $J_{4,5}$=6 Hz, 4-H), 4.53 (ddd, 1H, $J_{1,10\beta}$=9.5 Hz, $J_{1,10\alpha}$=5.5 Hz, $J_{1,7}$=1.5 Hz, 1-H), 4.68 (AB system, J=12 Hz, $ArCH_2$), 4.76 (dt, 1H, $J_{4,5}$=6 Hz, $J_{5,7}$=2.5 Hz, 5-H), 5.5 (d, 1H, $J_{3,4}$=1.5 Hz, 3-H), 6.28 (dd, 1H, $J_{5,7}$=2.5 Hz, $J_{1,7}$=1.5 Hz, 7-H), 7.33 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=26.17 (q), 27.53 (q), 28.31 (t), 35.22 (t), 64.21 (d), 69.81 (t), 71.25 (d), 74.71 (d), 96.18 (d), 110.35 (s), 126.24 (d), 127.71 (d), 127.97 (d), 128.08 (d), 136.74 (s), 158.40 (s), 197.22 (s).

5a: Treatment of **4a** (1.5 g, 4.3 mmol) with thionyl chloride (0.34 ml, 4.73 mmol) in pyridine (0.41 ml, 5.16 mmol) at 0 °C for 15 h yielded **5a** (0.95 g, 67%).

(1*S*,3*S*,4*S*,5*S*)-3-Benzyloxy-4,5-isopropylidenedioxy-2-oxabicyclo[4.4.0]dec-6-en-8-one (5b from 4b). Treatment of **4b** (1.8 g, 5.2 mmol) under the same conditions as described above yielded a yellow oil **5b** (1.1 g, 67%). $[\alpha]_D$ +6.38° (*c* 0.47, $CHCl_3$). Calcd for $C_{19}H_{22}O$ (MW 330): C, 69.09; H, 6.66%. Found: C, 69.15; H, 6.60%. CD (CH_3OH) $\Delta\xi_{343}$=−0.10; $\Delta\xi_{245}$=−2.64; $\Delta\xi_{215}$=+2.6. IR (film) ν_{max} 1690, 1550, 1500, 1380, 1240, 1150, 1050, 870, 800, 760, 700, 680 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.36 (s, 3H), 1.43 (s, 3H), 2.10 (m, 2H, 10-H), 2.45 (m, 2H, 9-H), 4.25 (dd, 1H, $J_{3,4}$=6.5 Hz, $J_{4,5}$=4 Hz, 4-H), 4.59 (d, 1H, J=12 Hz, $ArCH_2$), 4.63 (dd, 1H, $J_{1,10\beta}$=2.5 Hz, $J_{1,10\alpha}$=6 Hz, 1-H), 4.70 (dd, 1H, $J_{4,5}$=4 Hz, $J_{5,7}$=1.5 Hz, 5-H), 4.72 (d, 1H, $J_{3,4}$=6.5 Hz, 3-H), 6.08 (d, 1H, $J_{5,7}$=1.5 Hz, 7-H), 7.29 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=25.36 (q), 26.91 (q), 30.62 (t), 36.05 (t), 68.10 (d), 70.11 (t), 74.79 (d), 77.64 (d), 98.44 (d), 111.07 (s), 127.70 (d), 127.77 (d), 127.95 (d), 137.11 (s), 154.12 (s), 197.58 (s).

Hydrogenations. (1*R*,3*S*,4*S*,5*S*,6*S*)-3-Benzyloxy-4,5-isopropylidenedioxy-2-oxabicyclo[4.4.0]decan-3-one (6). Palladium on charcoal (10%) (35 mg) was added to a solution of **5a** (0.35 g, 1 mmol) in absolute ethanol (1 ml). The reaction mixture was shaken under a hydrogen atmosphere for 1 h. Filtration of the catalyst was followed by evaporation of the solvent to afford a colorless oil **7** (0.34 g, 97%); $[\alpha]_D$ +58.9° (*c* 1.9, $CHCl_3$). Calcd for $C_{19}H_{24}O_5$ (MW 332): C, 68.67; H, 7.22%. Found: C, 68.59; H, 7.17%. CD (CH_3OH) $\Delta\xi_{292}$=+0.14. IR (film) ν_{max} 1720, 1600, 1520, 1460, 1380, 1210, 1150, 1070, 1020, 760, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.39 (s, 3H), 1.52 (s, 3H), 1.89 (m, 1H, 10β-H), 2.27 (m, 1H, 10α-H), 2.42 (m, 1H, 6-H), 2.67 (m, 4H, 9-H+7-H), 4.15 (m, 1H, 1-H), 4.19 (d, 1H, $J_{4,5}$=7 Hz, 4-H), 4.47 (dd, 1H, $J_{4,5}$=7 Hz, $J_{5,6}$=6 Hz, 5-H), 4.72 (AB system, J=12 Hz, $ArCH_2$), 5.21 (s, 1H, 3-H), 7.34 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ=24.91 (q), 25.65 (q), 29.70 (t), 36.31 (d), 36.45 (t), 39.99 (t), 63.49 (d), 69.50 (t), 72.60 (d), 73.42 (d), 97.90 (d), 108.88 (s), 127.87 (d), 127.92 (d), 128.46 (d), 137.36 (s), 210.70 (s).

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11) The 2D NOE (bidimensional nuclear Overhauser enhancement) technique was used for assigning the cis configuration of the adjacent rings. Thus irradiation at δ=2.42 (6-H) affected the signal at δ=4.15 (1-H) showing the spatial proximity of both protons.