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REACTIONS OF CANNABINOID TOSYLHYDRAZONES

STEREOCHEMICAL ASPECTS

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Abstract Reactions of the epimeric 7-oxo-hexahydrocannabinol tosylhydrazone acetates (**2a** and **4a**) are described. Under aprotic basic reaction conditions followed by acetylation both compounds lead to the known $\Delta^{1(7)}$-tetrahydrocannabinol acetate (**6**); under protic conditions the axial isomer undergoes ring expansion (to **7b**), the equatorial one gives **6**.

We recently reported[1] that in the presence of base the stereochemical preference at C-1 of certain cannabinoids depends on the proximity of the free phenolic group. Thus in **1a**, unexpectedly, the isomer with the axial carbomethoxyl group predominates on basic equilibration; in **1b** (in which the phenolic group is blocked as an ether) the equatorial carbomethoxyl group is the major isomer. We were interested to find out whether the reactions in base of cannabinoids tosylhydrazones are likewise dependent on a proximal free phenolic group. While we have not been able to reach a definite conclusion on this point, we wish to report some interesting results in this series which throw light on the stereochemical requirements of the various reactions of cannabinoid tosylhydrazones in base.

The tosylhydrazone **2a**, in which the C-1 substituent is axial, was prepared by the reaction of tosylhydrazine with the appropriate 7-oxo-hexahydrocannabinol acetate (CO group axial) (**3**). The tosyl hydrazone **4a**, in which the C-1 substituent is equatorial was prepared from the respective (equatorial) aldehyde **5**. The aldehydes **3** and **5** were prepared by reduction of 7-oxo-Δ^6-THC acetate.[2]

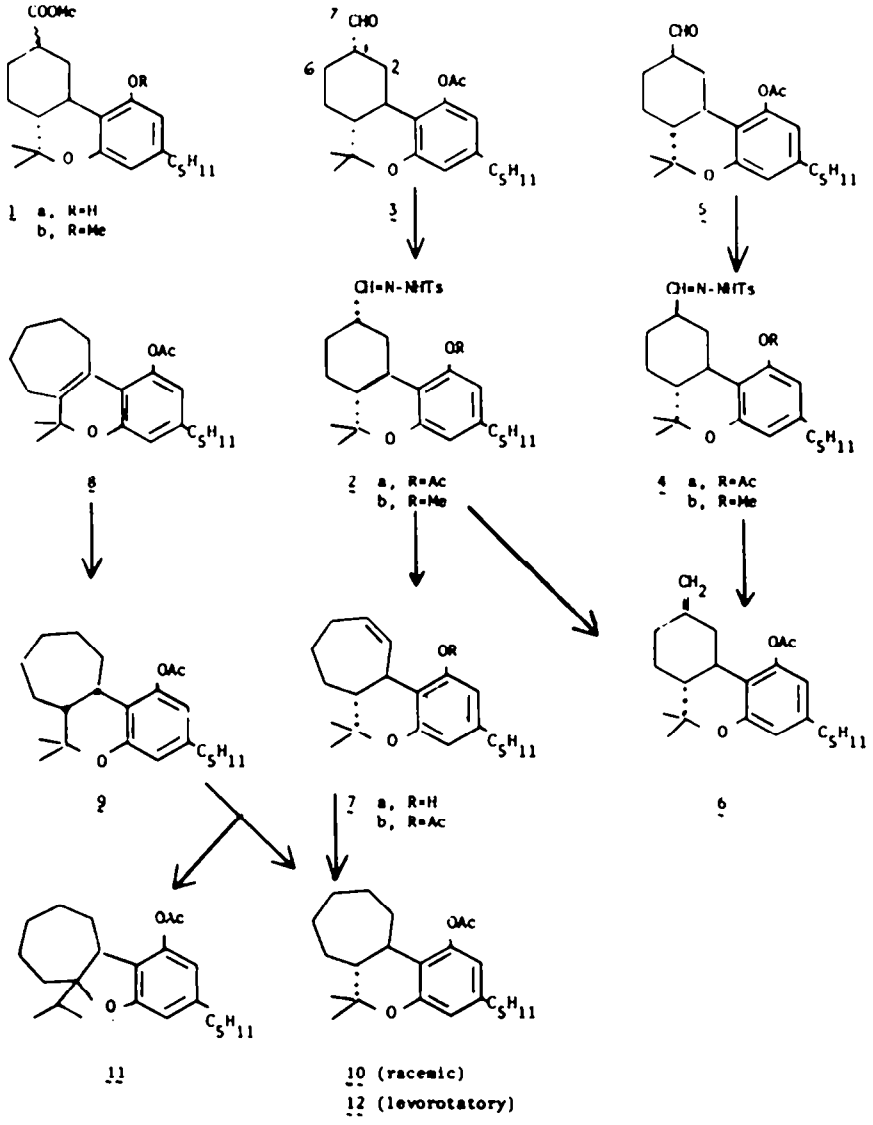
When either **2a** or **4a** were boiled with sodium methoxide in benzene or digylme ("aprotic" Bamford–Stevens reaction conditions[3]), followed by acetylation, only the known[4] $\Delta^{1(7)}$-THC acetate (**6**) was obtained (in 30–40% yield) in addition to starting material.

When **2a** was treated with the Na salt of ethylene glycol in boiling ethylene glycol ("protic" Bamford–Stevens reaction conditions[3]) followed by acetylation the major product obtained was **7b**, the result of a ring expansion.

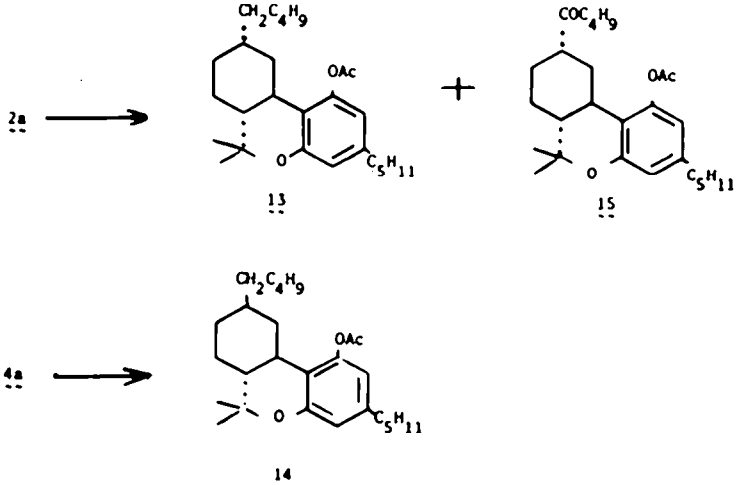
The structure of **7b** was determined as follows. The known[5] **8** was reduced by catalytic hydrogenation over Pd-C to the racemic **9**, in which the stereochemistry at the common carbons of the pyran and the cycloheptan rings is presumably *cis*, on the basis of the accepted *cis* addition of hydrogens on catalytic reduction. The reacemic, *cis* compound **9** was isomerized to racemic *trans* pyran **10** on treatment with aluminium trichloride, following known precedents.[6] In addition to **10** we obtained a further compound to which we assign the furan ring containing structure **11**, on the basis of spectral data. Of particular relevance to this proposed structure (**11**) are **a**, a six proton double doublet at δ, 9.12 which we assign to the methyl groups of the isopropyl moiety and **b**, the presence of a base peak at M$^+$-42 in the mass spectrum, which is typical for the loss of a tertiary isopropyl group. The formation of **11** is not unexpected, as the isomerization of **9** to **10** involves the cleavage of the pyran ring and formation of a cationic centre at the isopropyl tertiary carbon which can equilibrate with the adjacent tertiary carbon position on the cycloheptane ring.

Reduction of **7b** with hydrogen over Pd-C gave **12** which was shown to be the levorotatory form of above described **10**. The IR, NMR and MS spectra of **10** and **12** were identical. This correlation conclusively establishes the structure of the rearrangement product **7b**, except for the position of the double bond. This position was determined on the basis of the UV spectrum and by comparison of the NMR spectrum of **7b** with those of several related compounds (Table 1). Thus the UV spectrum indicates that the double bond in **7b** cannot occupy a position conjugated to the aromatic ring. Plausible mechanisms (see below) of the ring expansion reaction place the double bond at either the β,γ position (to the aromatic ring) or at a γ,δ-one. The latter position is tentatively excluded, as one would expect identical or close chemical shifts for both olefinic protons (*cf.* 7-nor-Δ^6 THC and its acetate in the Table 1). We prefer to place the double bond in the β,γ position on the basis of the considerable downfield shift of one of the olefinic protons (at δ 5.82) which is comparable to that in Δ^1-THC acetate (at δ 5.92), and is distinctively different from that of the olefinic proton in Δ^6-THC acetate (at δ 5.38) (Table 1). In the free phenol (**7a**) this olefinic proton moves upfield (to δ 6.17), as expected. The same phenomenon is observed with Δ^1-THC (δ 6.33) but is absent in Δ^6-THC (δ 5.35) or 7-nor-Δ^6-THC (Table 1). These relationships indicate that one of the olefinic protons in the rearrangement product **7b** is in the proximity of the phenolic group, which is compatible with a β,γ position of the double bond (as drawn) and not a γ,δ position.

While, as described above, the axial tosyl hy-

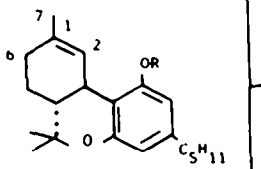
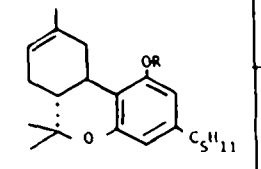
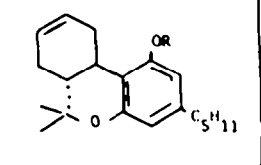
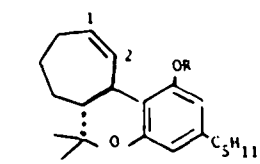


Scheme 1.



Scheme 2.

Table 1. NMR shifts of some cannabinoid olefinic protons

Compound		C-2 or C-6 H	C-1 H	Ref.
	R=H Δ^1-THC	6.35 (CCl_4)	—	7
	R=Ac Δ^1-THC acetate	5.92 (CCl_4)	—	8
	R=H Δ^6-THC	5.35 (CCl_4)	—	7
	R=Ac Δ^6-THC acetate	5.38 (CCl_4)	—	8
	R=H 7-nor-Δ^6-THC	5.78 ($CDCl_3$)	5.78 ($CDCl_3$)	9
	R=Ac 7-nor-Δ^6-THC acetate	5.74 ($CDCl_3$)	5.74 ($CDCl_3$)	12
	R=H 7a	6.17 ($CDCl_3$)	5.73 ($CDCl_3$)	see text
	R=Ac 7b	5.82 ($CDCl_3$)	5.56 ($CDCl_3$)	see text

drazone **2a** undergoes a rearrangement under the conditions of a "protic" Bamford Stevens reaction, the equatorial tosyl hydrazone (**4a**) undergoes an elimination under these conditions giving **6**. No rearranged product was isolated or observed on TLC.

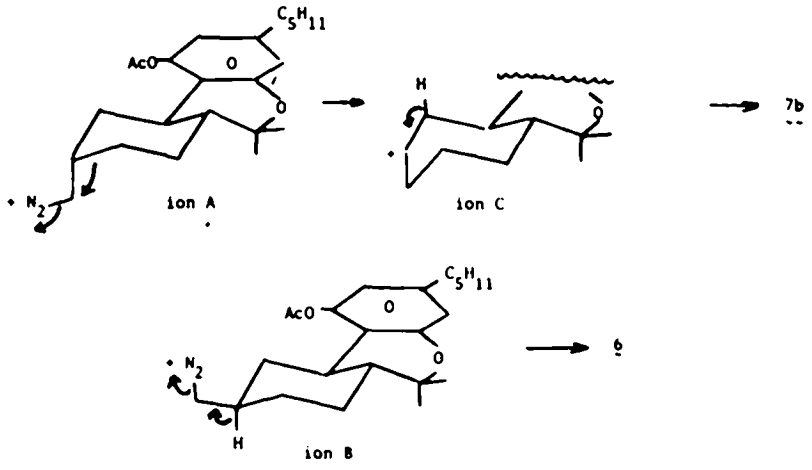
A further type of reaction takes place when the tosyl hydrazones **2a** and **4a** are reacted upon with excess butyllithium. An alkylation takes place leading to **13** and **14** respectively. In the reaction with **2a** in addition to **13** the oxo-cannabinoid **15** is also obtained.

When the methyl ethers **2b** and **4b** were submitted to the "protic" Bamford-Stevens reaction conditions, no identifiable products could be isolated probably due to initial demethylation. Hence it was impossible to verify our supposition as to the influence of the free phenolic group on reaction paths involving the "top" of the cannabinoid molecule (phenolic group, C-1, C-2, C-7).

The formation of an identical reaction product (**6**) from both the axial (**2a**) and equatorial (**4a**) tosyl hydrazones in the "aprotic" Bamford–Stevens reaction is to be expected on the basis of the carbenoid pathway generally assumed for this type of reaction.[3,10] The alkylation reactions of **2a** and **4a** are likewise unexceptional.[3,11] However the production of **7b** and **6** from **2a** and **4a** respectively under the "protic" Bamford–Stevens conditions is of some interest. Assuming that these reactions proceed though a cationic pathway, the respective diazonium ions, ion A and ion B, will be formed. Ion A is prone to ring expansion leading through ion C to **7b**. Ion B presumably gives **6** through concomitant loss of N_2 and the C-1 proton. This mechanism follows the accepted notion that in many reactions tosyl hydrazones decompose by concerted collapse of a diazonium ion.[3]

EXPERIMENTAL

Unless otherwise stated the following apply. UV measurements were made for solns in EtOH. IR spectra were taken in Nujol for crystalline compounds and as thin films on NaCl plates for oils. ^{1}H NMR data were determined in $CDCl_3$ with Me_4Si as internal standard. Tlc was performed on 0.2 mm precoated silica gel, $60F_{254}$ (Merck), and the plates were visualized with Fast Blue phenol reagent or by



Scheme 3.

charring with a soln of MeOH: H_2SO_4 (1:1). "Silica", used for chromatography means "Silica gel Woelm TSC for dry column chromatography." Mass spectra were obtained by direct inlet at 70 ev. "Worked up in the usual way" means addition of about 2 volumes of ether and 5 volumes of cold water, separation of the layers, washing the organic layer with a satd brine soln, drying over $MgSO_4$, filtration and evaporation to dryness *in vacuo*. "Acetylation in the usual way" means additon of acetic anhydride and pyridine (in a ratio of 1:2) (3-5 mL per reaction); the mixture is left overnight, poured onto ice, extracted with 50 mL ether, sequentially washed with 10% HCl, water, 10% NaOH, satd. brine soln, then dried over $MgSO_4$, followed by filtration and evaporation to dryness *in vacuo*.

Preparation of tosylhydrazones **4a** *and* **2a** *from aldehydes* **5** *and* **3**. The equatorial **5** (48 mg, 0.13 mmol) and tosyl hydrazine (24 mg, 0.13 mmol) were dissolved in MeOH (3 mL), the soln was heated to 40° on a water bath for 15 min and cooled to room temp. The volatiles were removed *in vacuo* and the crude product was chromatographed on silica. Elution with MeOH/$CHCl_3$ (5:95) gave the equatorial **4a** (50 mg, 71%), m.p. 136°; $[\alpha]_D$ − 74° (EtOH); NMR ($CDCl_3$)δ: 7.80 (dd, 2), 7.30 (dd, 2, J = 9.27 Hz), 7.06 (d, 1, J = 6.2Hz), 6.53 (s, 1), 6.37 (s, 1), 2.58 (m, 1), 2.48 (t, J = 7.8 Hz), 2.42 (s, 3), 2.14 (s, 3), 1.35 (s, 3), 1.05 (s, 3), 0.87 (t, J = 6.6 Hz, 3); MS *m/e* (% base peak) 540 (4, M⁺), 356 (31), 341 (18), 330 (18), 315 (30), 314 (28), 299 (25), 297 (19), 279 (35), 271 (26), 258 (16), 245 (22), 231 (31), 226 (21), 218 (21), 205 (26), 193 (33), 167 (100); UV (EtOH) λ_{max} 274 (ϵ 3015), 282 (ϵ 2570) nm; IR 1770, 1740, 1630, 1570, 1430, 1375, 1205, 1175, 1040 cm^{-1} (Found: C, 66.84; H, 7.66; Calc for $C_{30}H_{40}N_2SO_3$): C, 66.67, H, 7.41%).

The axial **3** (130 mg, 0.35 mmol) and tosyl hydrazine (73 mg, 0.38 mmol) were dissolved in MeOH (10 mL). The procedure was identical to that described above. The axial **2a** (140 mg, 74%) is an amorphous solid, $[\alpha]_D$ + 15° (EtOH); NMR ($CDCl_3$)δ: 7.84 (m, 2); 1.37 (m, 3), 6.51 (m, 1), 6.37 (m, 1), 2.84 (br. d, 1), 2.74 (br. s, 1), 2.49 (m, 3), 2.34 (s, 3), 2.27 (s, 3), 1.30 (s, 3), 0.87 (t, J = 6.6 Hz, 3), 0.79 (s, 3); MS *m/e* (% base peak) 356 (100), 340 (40), 314 (90), 299 (50), 297 (40), 226 (60). UV (EtOH) λ_{max} 274 (ϵ 2462), 283 (ϵ 2162) nm; IR 1760, 1730, 1620, 1560, 1420, 1360, 1200, 1160, 1030 cm^{-1}.

Synthesis of rearrangement products **7a,b**. The tosylhydrazone **2a** (60 mg, 0.11 mmol) was added under N_2 to a stirred soln of sodium ethylene glycol (prepared from 40 mg Na and 3 mL dry ethylene glycol). The soln was boiled under reflux for 30 min, cooled and worked up as usual. The crude product was acetylated in the usual way and the resulting oil was chromatographed on TLC plates (eluent 10% ether in petroleum ether b.p. 60-80°) to yield **7b** (15 mg, 38%), an oil, $[\alpha]_D$ − 94° (EtOH); NMR ($CDCl_3$)δ: 6.54 (s, 1), 6.45 (s, 1), 5.82 (br. s, 1), 5.56 (br. s, 1), 3.38 (br. s, 1), 2.53 (t, J = 5.6 Hz, 2), 2.19 (s, 3), 1.39 (s, 3) 1.07 (s, 3), 0.88 (t, J = 6.5 Hz, 3); MS *m/e* (% base peak) 356 (86, M⁺), 341 (31), 314 (100), 299 (78), 298 (55), 280 (8), 271 (58), 259 (36), 243 (66), 217 (47), 193 (44); UV (EtOH) λ_{max} 274 (ϵ 1350), 280 (ϵ 1424) nm; IR 1770, 1630, 1575, 1430, 1205, 1040 cm^{-1}.

In a separate experiment the acetylation step was left out to yield **7a**, (13 mg, 30%), an oil, $[\alpha]_D$ − 206° (EtOH); NMR ($CDCl_3$)δ: 6.30 (s, 1), 6.29 (s, 1), 6.17 (m, 1), 5.73 (m, 1), 4.82 (s, OH), 3.44 (m, 1), 2.48 (t, J = 5.7 Hz, 2), 1.40 (s, 3), 1.08 (s, 3), 0.89 (t, J = 6.9 Hz, 3); MS *m/e* (% base peak) 314 (100, M⁺), 299 (70), 271 (59), 258 (41), 243 (29), 217 (18), 193 (24). UV (EtOH) λ_{max} 273 (ϵ 1470), 282 (ϵ 1385) nm; IR 3400, 1620, 1575, 1420, 1170, 1030 cm^{-1}.

Preparation of Δ^7*-tetrahydrocannabinol acetate* (**6**) *from* **4a**. The tosylhydrazone **4a** (60 mg, 0.11 mmol) was added under N_2 to a soln of sodium ethylene glycol (prepared from 40 mg Na in 3 mL distilled ethylene glycol). The soln was boiled under reflux for 30 min, cooled, and worked-up in the usual way to yield **6** (20 mg, 56%); NMR ($CDCl_3$)δ: 6.56 (s, 1), 6.40 (s, 1), 4.73 (s, 1), 4.71 (s, 1), 3.22 (d, 1), 2.52 (m, 3), 2.31 (s, 3), 1.40 (s, 3), 1.05 (s, 3), 0.88 (t, J = 6.3 Hz, 3); MS *m/e* (% base peak) 356 (82, M⁺), 341 (26), 316 (46), 314 (100), 299 (72), 277 (38), 273 (44), 271 (46), 231 (62), 193 (38); IR 1775, 1630, 1570, 1430, 1380, 1210, 1040, 890 cm^{-1}.

In a similar manner **6** was obtained from **4a** under the above conditions with the following reagents: $NaOCH_3$/diglyme (56% yield), $NaOCH_3$/benzene (46% yield), and from **2a** using $NaOCH_3$/diglyme (43% yield) and $NaOCH_3$/benzene (77% yield).

Reduction of **7b** *to* **12**: Compound **7b** (20 mg, 0.056 mmol) was dissolved in EtOH (25 mL) and hydrogenated over Pd catalyst (20 mg, 10% Pd/C at 40 psi) overnight. The soln was filtered and the volatiles removed *in vacuo*. Chromatography on silica and elution with Et_2O/petroleum ether, b.p. 60-80°C (10:90), yielded **12** (17 mg, 85%), an oil; $[\alpha]_D$ − 85 (EtOH); NMR ($CDCl_3$)δ: 6.54 (s, 1), 6.43 (s, 1), 2.48 (t, J = 5.8 Hz, 2), 2.29 (s, 3), 1.39 (s, 3), 1.00 (s, 3), 0.88 (t, J = 6.0 Hz, 3); MS *m/e* (% base peak) 358 (65 M⁺), 316 (100), 301 (40), 299 (70), 273 (85), 260 (50), 245 (15), 231 (15), 217 (20), 206 (15), 193 (60); UV (EtOH) λ_{max} 277 sh (ϵ 2111), 285 (ϵ 2186) nm; IR 1770, 1630, 1575, 1430, 1370, 1205, 1035 cm^{-1}.

Preparation of compound **9** *from compound* **8**. Compound **8** (250 mg, 0.7 mmol) was dissolved in 35 cc EtOH to which Pd catalyst (250 mg, 10% Pd/C) was added and the mixture was hydrogenated in a Parr apparatus (40 psi, 24 hr). The soln was filtered and the volatiles were removed *in vacuo*. The crude product was chromatographed on silica and was eluted with Et_2O/petrol ether, 60-80° 10:90. Recrystallization from cold (−80°) pentane furnished pure **8** (174 mg, 69%); m.p. 58-59°; NMR ($CDCl_3$)δ: 6.56 (s, 1), 6.47 (s, 1), 2.85 (m, 1), 2.52 (t, J = 5.6 Hz, 2), 2.46 (s, 3),

1.37 (s, 3), 1.29 (s, 3), 0.90 (t, J = 5.0 Hz, 3); MS *m/e* (% base peak) 358 (39, M⁺), 343 (17), 316 (55), 300 (39), 273 (100), 260 (28), 245 (17), 231 (16), 217 (11), 207 (11), 193 (44); UV (EtOH) λ_{max} 275 (ε 2000), 281 (ε 2100) nm; IR 1770, 1630, 1580, 1430, 1380, 1210, 1040 cm^{-1}; (Found: C, 77.03, H, 9.62; Calc for $C_{22}H_{34}O_3$: C, 77.09, H, 9.50%).

Rearrangement of compound **9** *to compounds* **10** *and* **11**: Compound **9** (60 mg, 0.17 mmol) was dissolved in dry CH_2Cl_2 (5 mL), under dry N_2 and the soln was cooled to 0°. $AlCl_3$ (70 mg) was added, with stirring. The mixture was left overnight and worked-up in the usual manner. The mixture obtained was chromatographed on silica. Elution with 10% Et_2O in petroleum ether b.p. 60–80° gave **11** (35 mg, 58%) an oil; NMR ($CDCl_3$)δ: 6.45 (s, 1), 6.35 (s, 1), 3.36 (m, 1), 2.53 (t, J = 5.6 Hz, 2), 2.27 (s, 3), 0.91 (dd, J = 6.2 Hz, 6), 0.88 (t, J = 6.7 Hz, 3); MS *m/e* (% base peak) 358 (47, M⁺), 316, (47), 301 (8), 299 (17), 287 (5), 274 (100), 260 (8), 259 (9), 245 (7), 243 (9), 231 (5), 229 (7), 217 (17), 216 (15), 215 (12), 203 (16), 193 (40), 173 (25); UV (EtOH) λ_{max} 275_{sh} (ε 1790), 281 (ε 1731) nm; IR 1770, 1630, 1595, 1435, 1370, 1205, 1055 cm^{-1}. Further elution with the same eluent gave **10** (21 mg, 35%), an oil with spectral data identical to those of **12**, and significantly different (in particular the NMR spectrum) from those of the *cis* **9**.

Reductive alkylation of compound **4a** *to compound* **14**. The tosylhydrazone **4a** (60 mg, 0.11 mmol) was dissolved in dry Et_2O (3 mL) under N_2 and n-BuLi (0.3 mL, 0.7 mmol, 15% soln n-BuLi in hexane) was added with a syringe, with stirring. After 2 hr the mixture was worked-up and acetylated in the usual manner, to yield **14** (27 mg, 59%), an oil, $[\alpha]_D$ − 83° (EtOH); NMR ($CDCl_3$)δ: 6.54 (s, 1), 6.37 (s, 1), 2.70 (br. d, 1), 2.49 (t, J = 7.4 Hz, 2), 2.28 (s, 3), 1.36 (s, 3), 1.06 (s, 3), 0.89 (m, 6); MS *m/e* (% base peak) 414 (15, M⁺), 372 (23), 354 (7), 329 (13), 316 (15), 314 (13), 299 (11), 297 (11), 284 (10), 271 (11), 258 (13), 246 (23), 243 (16), 239 (18), 236 (36), 231 (18), 214 (56), 209 (100), 205 (49); UV (EtOH) λ_{max} 277_{sh} (ε 2171), 282 (ε 2240) nm; IR 1760, 1625, 1560, 1415, 1360, 1300, 1200 cm^{-1}.

Preparation of compounds **13** *and* **15** *from compound* **2a**. The tosylhydrazone **2a** (60 mg, 0.11 mmol) was dissolved in dry Et_2O (4 mL) under N_2 and n-BuLi (0.3 mL, 0.71 mmol, 15% in hexane) was added with a syringe. After 2 hr the mixture was worked up and acetylated in the usual manner. Chromatography on silica (elution with 10% Et_2O in petroleum ether b.p. 60–80°) yielded **13** (20 mg, 44%) an oil, $[\alpha]_D$ − 74 (EtOH); NMR ($CDCl_3$)δ: 6.55 (s, 1), 6.39 (s, 1), 2.50 (m, 4), 2.29 (s, 3), 1.35 (s, 3), 1.07 (s, 3), 0.89 (m, 6); MS *m/e* (% base peak) 414 (65, M⁺), 372 (100), 355 (64), 328 (90), 316 (41), 301 (12), 299 (6), 289 (6), 287 (4), 273 (4), 259 (9), 245 (12), 231 (15), 217 (17), 193 (85); UV (EtOH) λ_{max} 277_{sh} (ε 1804), 283 (ε 2015) nm; IR 1770, 1630, 1560, 1420, 1365, 1305, 1200, 1130, 1030 cm^{-1}. Further chromatography with the same eluent gave **15** (5 mg oil, 11%); $[\alpha]_D$ − 90 (EtOH); NMR ($CDCl_3$)δ: 6.57 (s, 1), 6.36 (s, 1), 2.84 (br. d, 1), 2.46 (m, 5), 2.28 (s, 3), 1.37 (s, 3), 1.07 (s, 3), 0.91 (t, J = 6.9 Hz, 3), 0.875 (t, J = 5.9 Hz, 3); MS *m/e* (% base peak) 428 (31, M⁺), 413 (4), 386 (100), 371 (8), 369 (11), 342 (12), 330 (30), 301 (11), 287 (4), 285 (3), 283 (6), 263 (7), 257 (5), 245 (11), 235 (4), 231 (10), 219 (8), 217 (7), 207 (10), 193 (38); UV (EtOH) λ_{max} 275 (ε 1815), 286 (ε 1849) nm; IR 1770, 1710, 1620, 1560, 1420, 1360, 1200, 1125, 1025 cm^{-1}.

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