

Improved Conversion of 6-*endo*-Tosyloxybicyclo[2.2.2]octan-2-ones into 6-*exo*-Acetoxy and 6-*exo*-Benzoyloxybicyclo[2.2.2]octan-2-ones¹⁾

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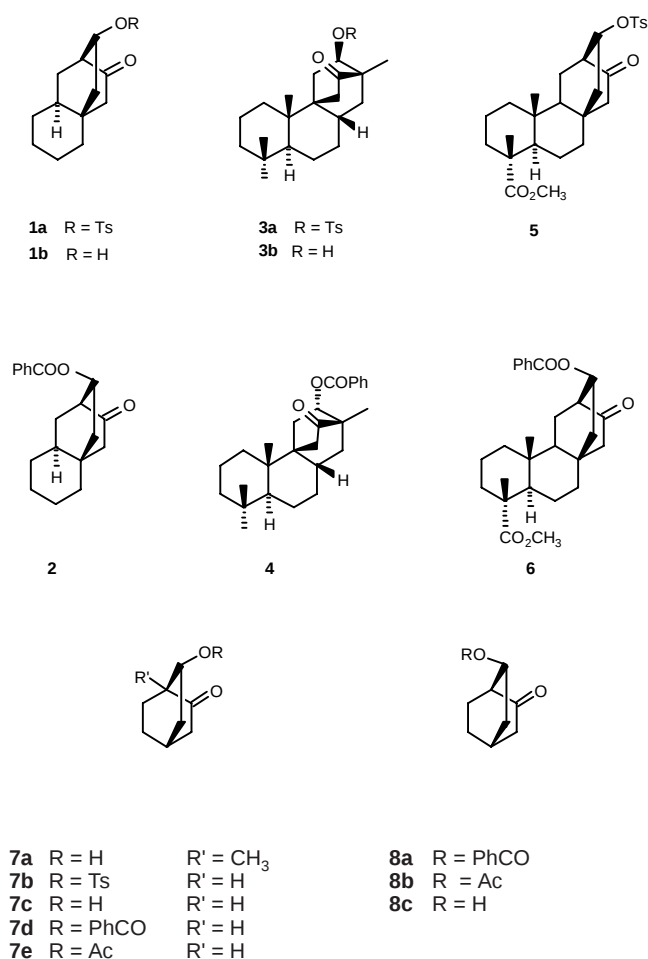
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Abstract. The reaction conditions for the conversion of 6-*endo*-tosyloxybicyclo[2.2.2]octan-2-one (**7b**) into 6-*exo*-acetoxy (**8b**) and 6-*exo*-benzoyloxybicyclo[2.2.2]octan-2-one (**8a**), respectively, were improved. Thus known 6-*endo*-tosyloxy-bicyclo[2.2.2]octan-2-ones ($\pm$)- (1*RS*,6*SR*,8*SR*,11*RS*)-11-[(4-toluenesulfonyl)oxy]tricyclo[6.2.2.0^{1,6}]dodecan-9-one (**1a**), 13-methyl-15-oxo-9 β ,13 β -ethano-9 β -podocarpin-12 α -yl benzoate (**3a**), and methyl (13*S*)-13-(benzoyloxy)-16-oxo-17-[(4-

tolylsulfonyl)oxy]-17-noratisan-18-oate (**5**), were converted, in comparable yields, as previously recorded, but much shorter times, into ($\pm$)- (1*RS*,6*SR*,8*SR*,11*SR*)-11-(benzoyloxy)tricyclo[6.2.2.0^{1,6}]dodecan-9-one (**2**), 13-methyl-15-oxo-9 β ,13 β -ethano-9 β -podocarpin-12 α -yl benzoate (**4**), and methyl (13*S*)-13-(benzoyloxy)-16-oxo-17-noratisan-18-oate (**6**), respectively.

Some years ago, in the frame of the syntheses of the diterpenes (+)-18-deoxystemarin [**1a**] and (+)-methyl trachyloban-18-oate [**1b**], we reported the conversion of 6-*endo*-tosyloxybicyclo[2.2.2]octan-2-ones **1a**, **3a** and **5** into 6-*exo*-benzoyloxybicyclo[2.2.2]octan-2-ones **2**, **4** and **6**, respectively.

These conversions were achieved – slightly modifying a method previously described for acyclic [**2a**, **2b**, **3**] and cyclic secondary alcohols [**2c**, **3**] – by refluxing for about 24 hours, in the presence of tetraethylammonium benzoate (TEAB) [**5**], solutions of **1a** and **3a** in acetone and of **5** in THF. In the same paper, we pointed out the importance of this conversion, in that it enlarges the number of available substituted bicyclo[2.2.2]octan-2-ols and thus that of compounds obtainable from them by solvolytic rearrangement of suitable derivatives [**8**]. Despite several known procedures for the inversion of configuration of secondary alcohols, based on the transformation of the hydroxyl group in a better nucleofuge [**9**], they were not applied to this class of compounds, probably because of the above mentioned tendency to rearrangement of 2-leaving group substituted bicyclo[2.2.2]octanes. An inversion methodology for such a class of alcohols would have been very advantageous in previous natural products syntheses [**7**, **8i**]. Aiming to overcome this difficulty, we hypothesized [**1a**] that a carbonyl group adjacent to the bridgehead C-atom, such as in 6-*endo*-hydroxybicyclo[2.2.2]octan-2-ones, the major products of the acid catalyzed intramolecular aldol condensation of 3-oxocyclohexanecarbaldehydes



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[10, 11], might have prevented the development of a positive charge on that C-atom and thus the rearrangement [12]. Since 6-*exo*-hydroxybicyclo[2.2.2]octan-2-ones might equilibrate, through a retroaldol–aldol reaction, with their *endo* epimers and since this equilibrium is shifted towards the latter epimer [7, 10, 15], we looked for a nucleophile, such as the carboxylate ion, which would have provided a protected hydroxyl group at C(6), locking in this way the ketol system.

We wish now to describe an improvement of this procedure, which resulted in a dramatic shortening of the reaction time. A well defined experimental protocol is also reported.

Results and Discussion

The experiments we carried out are summarized in Tables 1 and 2. **7b**, the simplest 6-*endo*-tosyloxybicyclo[2.2.2]octan-2-one, was chosen as a tool.

Four tetraalkylammonium carboxylates were used: the already mentioned TEAB, tetraethylammonium acetate (TEAA), tetrabutylammonium benzoate (TBAB) and tetrabutylammonium acetate (TBAA). All reactions resulted very clean and provided in excellent yields compounds **8a** or **8b**, depending on the salt used.

Compounds **8a** and **8b** were identical to the products prepared from 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one (**8c**) [10, 15e] by the action of benzoyl chloride and acetic anhydride in pyridine, respectively; besides **8a** was different from **7d**, the benzoyl derivative of **7c** [10], and **7e** from **8b**, the acetyl derivative of **7c**.

The experiments reported in Table 1, entries 1 → 8, were carried out at reflux at a 0.05M salt concentration

and at a 1/4 substrate/salt ratio. Owing to the reduced solubility, as compared to acetone, of TEAB and TEAA in THF and benzene, the experiments reported in entries 5 → 8 were carried out only with TBAB [16] and TBAA [17]. The recorded reaction times show a dependence upon the tetraalkylammonium cation and the solvent.

The experiments described in entries 1 → 8 allowed also to ascribe a less effective role to the carboxylate ion. Those reported in Table 1, entries 9 → 12, were carried out in the attempt of further reducing the reaction times; as expected, an acceleration of the inversion process and a solvent effect paralleling that reported in entries 5 → 8 was observed when the reactions were performed with TBAB and TBAA in THF and benzene, respectively, at a 0.1M salt concentration and at a 1/4 substrate/salt ratio. Finally, we ascertained that comparable results can be obtained also at lower substrate/salt ratios and that toluene can be used as the solvent instead of benzene (Table 1, entry 11). When these conditions were applied to known 6-*endo*-tosyloxybicyclo[2.2.2]octan-2-ones **1a**, **3a** and **5** (Table 2), we were able to obtain the corresponding epimeric *exo* carboxylates **2** [1a], **4** [1a] and **6** [1b] in comparable yields but in much shorter reaction times.

Table 2 Inversion reactions with TBAB on substituted 6-*endo*-tosyloxybicyclo[2.2.2]octan-2-ones ^{a)}

entry	substrate	product	conversion time (min)
1	1a	2	30
2	3a	4	15
3	5	6	30

^{a)} All reactions were carried out in benzene at reflux. Isolated yields ranged from 83 to 90%. Salt concentration = 0.1M; substrate/TBAB ratio = 1/4.

The above reported results are, in our opinion, of general interest, since the conversion of 6-*endo*-hydroxybicyclo[2.2.2]octan-2-ones into their epimeric esters is a process sought also by other authors as well as the nucleophilic displacement by means of tetraalkylammonium carboxylates.

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Experimental

All reactions were carried out under an argon atmosphere in a carefully flamed glassware. All solvents were dried over standard drying agents and distilled just before use. TEAA (Aldrich), TBAA and TBAB (Fluka) were used as such. Before TEAB became commercially available (Fluka), it was

Table 1 Reactions of **7b** with tetraethyl and tetrabutylammonium carboxylates in various solvents ^{a)}

entry	solvent	salt	product	conversion time (min)
1	acetone	TEAB ^{b)}	8a	1320
2	acetone	TEAA ^{b)}	8b	1140
3	acetone	TBAB ^{b)}	8a	420
4	acetone	TBAA ^{b)}	8b	450
5	THF	TBAB ^{b)}	8a	50
6	THF	TBAA ^{b)}	8b	45
7	benzene	TBAB ^{b)}	8a	20
8	benzene	TBAA ^{b)}	8b	20
9	THF	TBAB ^{c)}	8a	30
10	THF	TBAA ^{c)}	8b	30
11	benzene	TBAB ^{c,d,e)}	8a	12
12	benzene	TBAA ^{c)}	8b	15

^{a)}All reactions were carried out at reflux. Isolated yields ranged from 84 to 90%. ^{b)} Salt concentration = 0.05 M; **7b**/salt ratio = 1/4.

^{c)} Salt concentration = 0.1M; **7b**/salt ratio = 1/4. ^{d)} When this reaction was performed with 1/2 and 1/1 **7b**/salt ratios, the conversion was complete after 12 min and 30 min respectively. ^{e)} The same result was obtained performing this experiment in toluene at 80 °C.

prepared according to [18]. Reactions were monitored by TLC on 60-F 254 silica gel and visualized by spraying the TLC plates with a 2N H₂SO₄ solution followed by heating, or pouring the TLC in an I₂ chamber. Column chromatography was performed using silica gel 60, 70–230 mesh ASTM. Elemental analyses: EA 1110 CHNS–O analyzer, Carlo Erba Instruments. IR Spectra: Perkin Elmer-298 and Shimadzu-470 scanning infrared spectrophotometers, in cm⁻¹. ¹H and ¹³C NMR spectra: Varian-Gemini 200 instrument, in CDCl₃, δ in ppm rel. to internal Me₄Si (δ = 0 ppm), J in Hz. GC-MS analyses: Hewlett Packard 5890 gas chromatograph equipped with a HP 5971A mass selective detector.

The preparations of tosylates **1a**, **3a**, **5** have been previously described [1a, 1b].

6-*endo*-Tosyloxybicyclo[2.2.2]octan-2-one (**7b**)

To a stirred soln. of **7c** [10, 15e] (500 mg, 3.57 mmol) in pyridine (2 mL), cooled to 0 °C, TsCl (945 mg, 4.96 mmol) was added. The reaction mixture was stirred for 24 h at that temperature. H₂O (1 mL) was then added. After additional 10 min stirring, the whole was taken up with Et₂O (50 mL) and poured into a separatory funnel. The org. layer was washed with 2N HCl, H₂O, NaHCO₃ sat. soln., H₂O (till neutral), brine, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel column chromatography (petroleum ether 40–70 °C/Et₂O, 1:1) to give **7b** in 79% yield. TLC (petroleum ether 40–70 °C/Et₂O, 2:8): R_f (**7b**) > R_f (**7c**). *m.p.* (benzene/hexane): 127.5–128.5 °C. – IR (CCl₄): ν/cm^{-1} = 2950, 1735, 1384, 1182. – ¹H NMR (CDCl₃): δ/ppm = 1.40–1.90 (m, 5H), 2.10–2.35 (m, 4H), 2.35–2.50 (m, 4H), 4.95 (m, 1H), 7.33 (XX' of AA'XX', J = 8.2, 2H), 7.75 (AA' of AA'XX', J = 8.2, 2H). – ¹³C NMR (CDCl₃): δ/ppm = 20.2, 21.7, 23.3, 27.6, 34.3, 44.3, 47.3, 78.6, 127.7, 129.9, 134.0, 144.9, 211.2.

C ₁₅ H ₁₈ O ₄ S	Calcd.: C 61.21	H 6.17	S 10.87
(294.4)	Found: C 61.08	H 6.14	S 10.55.

Preparation of **8a** and **8b** (General Procedure)

A 25 mL double necked round-bottom flask, equipped with a reflux condenser, argon inlet and magnetic stirring bar, containing a 0.1M solution (7 mL) of the suitable tetraalkylammonium carboxylate in the desired solvent was dipped into an oil bath pre-heated to the solvent reflux temperature. After reflux started, **7b** (50 mg, 0.17 mmol) was added while stirring; the resulting mixture was refluxed until all the starting material had been consumed. The reaction mixture was then cooled to r.t. and diluted with H₂O (5 mL); the org. layer was separated and the aqueous one extracted with Et₂O (2 × 20 mL). Combined org. extracts were washed with brine and then dried (Na₂SO₄). After solvent removal under reduced pressure and silica gel column chromatography (petroleum ether 40–70 °C/Et₂O, 7:3), compounds **8a** (or **8b**) were obtained, in yields ranging from 84 to 90%. TLC (petroleum ether 40–70 °C/Et₂O, 1:1): R_f (**8a**) > R_f (**8b**) > R_f (**7b**).

6-*exo*-Benzoyloxybicyclo[2.2.2]octan-2-one (**8a**)

oil. – IR (CCl₄): ν/cm^{-1} = 3100, 2960, 1725, 1696, 1281, 1101. – ¹H NMR (CDCl₃): δ/ppm = 1.60–2.35 (2 m, 9H), 2.70–2.80 (m, 1H), 5.25–5.40 (m, 1H), 7.35–7.70 (m, 3H), 8.00–8.20 (m, 2H). – ¹³C NMR (CDCl₃): δ/ppm = 16.7, 23.9,

27.2, 34.4, 43.5, 47.5, 68.6, 128.6, 129.7, 130.3, 133.3, 165.9, 214.0. – EI-MS: 244 (M⁺).

C ₁₅ H ₁₆ O ₃	Calcd.: C 73.74	H 6.61
(244.3)	Found: C 74.04	H 6.61.

6-*exo*-Acetoxybicyclo[2.2.2]octan-2-one (**8b**)

oil. – IR (CCl₄): ν/cm^{-1} = 2950, 1739, 1251, 1230. – ¹H NMR (CDCl₃): δ/ppm = 1.50–1.85 (m, 4H), 2.05 (s, 3H), 2.10–2.30 (m, 5H), 2.50–2.60 (m, 1H), 5.00–5.10 (m, 1H). – ¹³C NMR (CDCl₃): δ/ppm = 16.7, 21.2, 24.1, 27.3, 34.3, 43.6, 47.6, 68.0, 170.2, 213.7. – EI-MS: 182 (M⁺).

C ₁₀ H ₁₄ O ₃	Calcd.: C 65.90	H 7.75
(182.2)	Found: C 66.18	H 8.08.

6-*endo*-Acetoxybicyclo[2.2.2]octan-2-one (**7e**)

To a stirred soln. of **7c** (100 mg, 0.71 mmol) in pyridine (2 mL), acetic anhydride (0.9 mL, 0.9 mmol) was added. The mixture was stirred overnight. H₂O (1 mL) was then added; after 10 min. of additional stirring, the whole was taken up with Et₂O (30 mL) and poured into a separatory funnel; the org. layer was then washed with 2N HCl, H₂O, NaHCO₃ sat. soln., H₂O (till neutral), brine, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel column chromatography (petroleum ether 40–70 °C/Et₂O, 1:1) to give **7e** in 90% yield. TLC (petroleum ether 40–70 °C/Et₂O, 2:8): R_f (**7e**) > R_f (**7c**). oil. – IR (CCl₄): ν/cm^{-1} = 2950, 1738, 1251, 1229. – ¹H NMR (CDCl₃): δ/ppm = 1.45–1.80 (2 m, 4H), 1.91 (s, 3H), 2.10–2.25 (m, 5H), 2.44 (q, J = 3, 1H), 5.05–5.12 (m, 1H). – ¹³C NMR (CDCl₃): δ/ppm = 19.9, 21.0, 23.4, 27.4, 33.8, 44.2, 46.6, 70.9, 170.0, 213.2. – EI-MS: 182 (M⁺).

C ₁₀ H ₁₄ O ₃	Calcd.: C 65.90	H 7.75
(182.2)	Found: C 65.70	H 7.84.

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