

Elusive 6-*exo*-Hydroxybicyclo[2.2.2]octan-2-ones from the Corresponding Acetates by Methanolysis in the Presence of CH₃ONa/La(OTf)₃

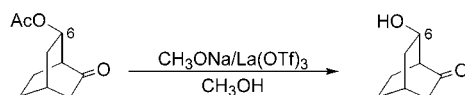
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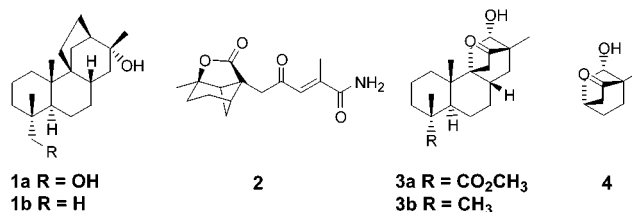
ABSTRACT



A series of 6-*exo*-acetoxycyclo[2.2.2]octan-2-ones were converted into the corresponding 6-*exo*-hydroxycyclo[2.2.2]octan-2-ones by methanolysis in the presence of CH₃ONa/La(OTf)₃. Under the given conditions, epimerization at C(6) of the latter led in the least favorable cases only to traces of the more stable 6-*endo*-hydroxycyclo[2.2.2]octan-2-ones. This procedure, when combined with the described conversion of easily available 6-*endo*-hydroxycyclo[2.2.2]octan-2-ones into the corresponding 6-*exo*-acetoxycyclo derivatives, provides a convenient route to elusive 6-*exo*-hydroxycyclo[2.2.2]octan-2-ones. Applications to total synthesis are shown and envisaged.

6-*exo*-Hydroxycyclo[2.2.2]octan-2-ones are key intermediates in the syntheses of the tetracyclic diterpenic diol stemarin **1a**¹ and bioactive sesquiterpenoid pinthunamide **2**,² obtained via intermediates **3a** and **4**, respectively. Given that **3a** and **4** were obtained as minor products of intramolecular aldol condensation of a 3-oxocyclohexanecetaldehyde,³ the above-mentioned syntheses suffer from an inefficient nondiastereoselective step. To the best of our knowledge, no efficient

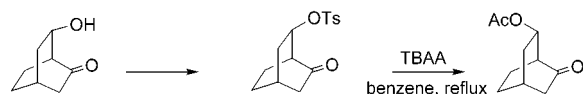
preparation of compounds **3a** and **4**, and of 6-*exo*-hydroxycyclo[2.2.2]octan-2-ones in general, is available as yet.



As a solution to this synthetic problem, we describe here an efficient conversion of 6-*exo*-acetoxycyclo[2.2.2]octan-2-ones into 6-*exo*-hydroxycyclo[2.2.2]octan-2-ones with virtually complete retention of configuration at C(6). The former compounds are easily obtained from 6-*endo*-hydroxy-

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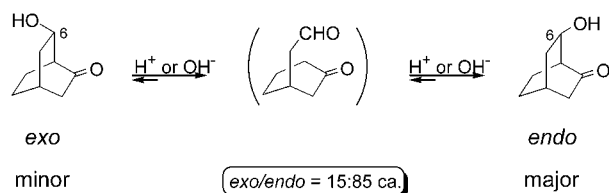
Scheme 1. Conversion of 6-*endo*-Hydroxybicyclo[2.2.2]octan-2-ones into 6-*exo*-Acetoxibicyclo[2.2.2]octan-2-ones



bicyclo[2.2.2]octan-2-ones⁴ (Scheme 1), which in turn are the major products of the aldol condensation of 3-oxocyclohexaneacetaldehydes.³

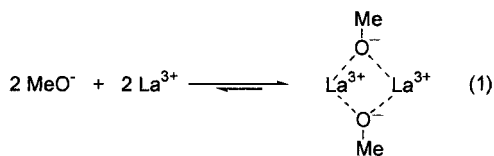
Given the facile conversion of 6-*exo*-hydroxybicyclo[2.2.2]octan-2-ones into the more stable *endo* C(6) epimers under basic or acid conditions (Scheme 2), the cleavage of the ester

Scheme 2. *exo*–*endo* Equilibration of 6-Hydroxybicyclo[2.2.2]octan-2-ones under Either Basic or Acid Conditions



bond of 6-*exo*-acetates without affecting the configuration at C(6) is by no means trivial and obviously cannot be carried out according to the available standard methods for the deprotection of acetylated hydroxyls.

In a recent paper, Brown and co-workers reported on the strong catalysis in the methanolysis of both aryl and alkyl esters by a La^{3+} -based catalyst.⁵ The active form of the catalyst was convincingly argued to be a dimethoxy-bridged dimer of stoichiometry $(\text{La}^{3+})_2(\text{MeO}^-)_2$, generated in situ upon mixing equimolar amounts of MeONa and $\text{La}(\text{OTf})_3$ in MeOH (eq 1) and having maximum catalytic activity in the neighborhood of neutral pH.



Thus, the dimeric species $(\text{La}^{3+})_2(\text{MeO}^-)_2$ features metal-complexed methoxide ions of very low Brönsted basicity but most active in the ester cleavage process because nucleophilic addition to the carbonyl is strongly assisted by the electrophilic La^{3+} partner. On this basis it was thought that in the presence of $(\text{La}^{3+})_2(\text{MeO}^-)_2$ 6-*exo*-acetoxibicyclo-

[2.2.2]octan-2-ones could undergo ester interchange with little or no concurring base-catalyzed epimerization at C(6).

In fact, Figure 1 shows that **4** was converted into its *endo*-

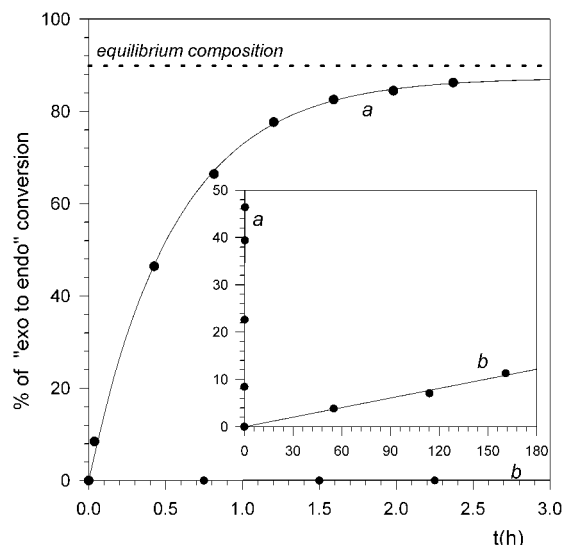


Figure 1. Equilibration of a 10.0 mM solution of **4** carried out in CD_3OD at 25 °C: (a) in the presence of 10.0 mM CD_3ONa alone, and (b) in the presence of 10.0 mM $\text{CD}_3\text{ONa}/\text{La}(\text{OTf})_3$. The reactions were followed by a 200 MHz ^1H NMR spectrometer using benzene as internal standard.

epimer at an exceedingly low rate under the given conditions. The estimated half-life is 42 days, compared with a half-life of 23 min in the presence of MeONa alone.

A number of 6-*exo*-acetoxibicyclo[2.2.2]octan-2-ones (**5**–**9**)^{6,7} were therefore subjected to methanolysis in the presence of the lanthanum catalyst. In a typical run 10.0×10^{-2} mmol of *exo*-ester was dissolved in 1.0 mL of a dry methanol⁸ solution 10.0 mM in $\text{La}(\text{OTf})_3$ and 9.5 mM in CH_3ONa .⁹ The reaction

(6) Compounds **6**, **7** (oil), **8** and **9** gave satisfactory elemental analyses. Owing to the small amount of material available, recrystallization of compounds **6**, **8**, and **9** was not attempted.

(7) Acetates **6**–**9** were prepared according to ref 4 from the proper 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one via the corresponding tosylate (Scheme 1). **Data for 6:** ^1H NMR (200.13 MHz) δ 4.82–4.68 (m, 1H), 2.40–0.88 (15H); ^{13}C NMR (50.32 MHz) δ 214.2, 170.4, 71.5, 47.2, 43.5, 35.5, 26.8, 24.7, 24.2, 21.0, 16.0; IR 1738 cm^{-1} . **Data for 7:** ^1H NMR (200.13 MHz) δ 5.05–4.95 (m, 1H), 2.47–2.42 (m, 1H), 2.09–1.10 (18H); ^{13}C NMR (50.32 MHz) δ 213.3, 172.2, 68.8, 52.3, 48.3 37.1, 36.5, 35.3, 33.2, 29.9, 25.8, 25.4, 21.1, 21.0; IR 1749.0, 1736.0 cm^{-1} . **Data for 8:** ^1H NMR (200.13 MHz) δ 5.01–4.96 (m, 1H), 3.63 (s, 3H), 2.55–2.50 (m, 1H), 2.05–0.87 (28H); ^{13}C NMR (50.32 MHz) δ 213.1, 179.0, 170.1, 68.3, 54.9, 51.9 51.3, 50.0, 48.3, 47.2, 38.5, 37.9, 37.4, 36.8, 36.6, 36.2, 21.1, 21.09, 18.7, 17.1, 16.4, 15.1; IR 1741.0, 1723.0 cm^{-1} . **Data for 9:** ^1H NMR (200.13 MHz) δ 4.73–4.67 (m, 1H), 2.24–0.83 (m, 33H); ^{13}C NMR (50.32 MHz) δ 215.2, 170.6, 72.3, 47.1, 45.9, 44.0, 42.0, 41.8, 38.6, 34.1, 33.2, 33.1, 33.0, 32.8, 31.3, 30.7, 22.3, 22.2, 21.2, 18.6, 15.8; IR 1740.0, 1737.0 cm^{-1} .

(8) Absolute methanol was distilled from Mg shavings and subsequently from CuSO_4 powder. The solvent was stored and handled under an argon atmosphere.

(9) $\text{La}(\text{OTf})_3$ was purchased by Aldrich and used as such. CH_3ONa methanol solutions were prepared by adding sodium to absolute methanol. Titrations of the above solutions with standard N/100 HCl Normex showed the absence of carbonate ions. CH_3ONa was added slightly in deficit to minimize the concentration of free methoxide ion in solution.


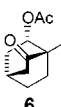
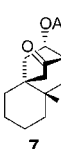
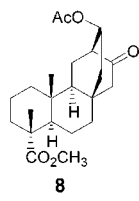
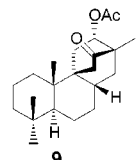
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mixture was kept at room temperature for the required time, quenched with cold 0.1 M phosphate buffer (pH 7.2), and thoroughly extracted with CH₂Cl₂.

Analysis of the reaction mixtures was carried out by HPLC (AcOEt/*n*-hexane on Nucleosil 105/5 EC 250/4 SiO₂ column). The results are reported in Table 1. In all cases

Table 1. Methanolyses of 10.0 mM Solutions of 6-*exo*-Acetoxycyclo[2.2.2]-octan-2-ones Carried Out in the Presence of 9.5/10.0 mM MeONa/La(OTf)₃ (CH₃OH, 25 °C)

entry	Starting <i>exo</i> -ester	time	Conversion (%)	<i>exo/endo</i> ketol ratio ^{a,b}
1		3 h	100	100/0
2		24 h	100	98/2
3		6 h	100	99/1
4		43 h	97	96/4
5		6 d	100	96/4

^a Epimers identified by comparison with authentic samples previously obtained in our laboratory by unambiguous routes: entry 1, refs 1 and 11; entry 2, ref 2 and references therein; entries 3 and 5, ref 10a; entry 4, ref 10b. ^b Error limits are on the order of $\pm 0.5\%$.

conversion of the *exo*-ester reactant into the corresponding ketol was quantitative or very nearly so, with very little or

no epimerization at C(6). The time required to achieve quantitative conversion into products increases considerably in the presence of a methyl group at the bridge-head carbon and/or further annulation and substitution. These results are in line with Brown's observation⁵ that the (La³⁺)₂(MeO⁻)₂-catalyzed methanolysis of esters is much more sensitive to steric effects than methanolysis catalyzed by methoxide alone.

The study was also extended to the corresponding benzoates,¹⁰ which required higher temperatures and longer reaction times. The net result was that under the more drastic conditions, as a result of their reduced reactivity compared with that of the corresponding acetates, the *exo*–*endo* equilibration was more significant and caused loss of any practical convenience.

In view of the facile preparation of **6** from the corresponding 6-*endo*-hydroxycyclo[2.2.2]octan-2-one (Scheme 1), obtaining **4**¹² from **6** improves a key step in the synthesis of (+)-pinthunamide **2** by Mori and co-workers² and suggests that a similar improvement could be achieved in the stemarin **1** synthesis by Kelly and co-workers.¹

The conversion of **3b**, the methanolysis product of **9**, into 18-deoxystemarin **1b**, realized in the course of this work as described by Kelly and co-workers for the conversion of **3a** into **1a**,¹ further supports this hypothesis.

In conclusion, we have shown how the results of an important mechanistic investigation can be translated into a new ad hoc methodology that, by solving a particular synthetic problem, can significantly enhance the overall efficiency of a multistep synthetic sequence.

Further applications and developments of the (La³⁺)₂(MeO⁻)₂ catalyst are under current investigation.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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