

β -Pinene-6-one: a Pivotal Synthetic Intermediate

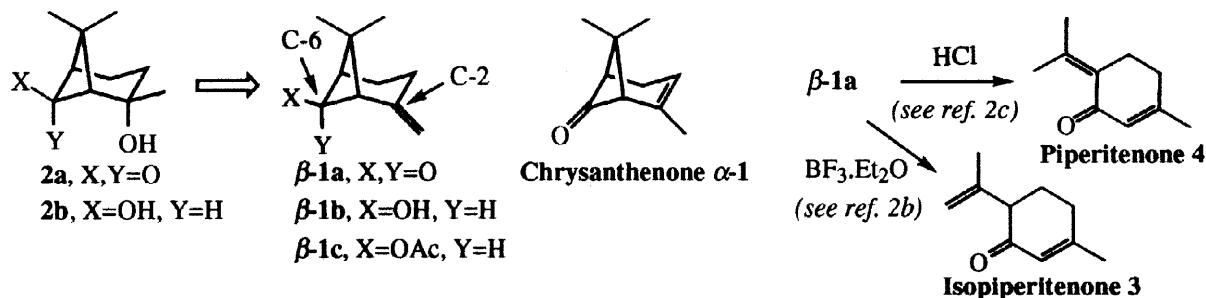
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Abstract: Submitting the title ketone to either acetoxymercuration or basic conditions resulted in the formation of the acid β -5 and α -5, respectively, with an useful selectivity, related rearrangements being observed by using the corresponding alcohol and its epoxy derivative. © 1998 Published by Elsevier Science Ltd. All rights reserved.

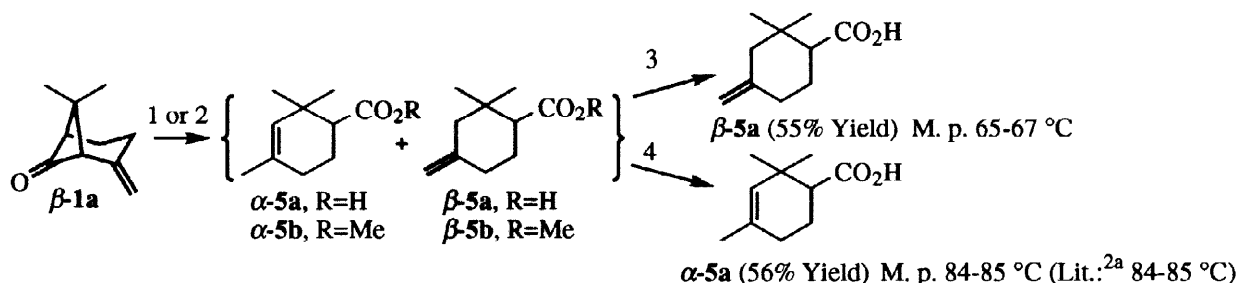
In the course of another work, we faced to the problem of converting pinene-6-one β -1a into hydroxypinanone 2a.¹ Unlike its α isomer (chrysanthenone α -1), whose chemical properties have been relatively well investigated,^{2a} the ketone β -1a has received little attention. Indeed, the only substantial, relevant, report we found was a paper by Snider, showing *inter alia* that β -1a rearranges into either pure isopiperitenone 3 or mixture of 3 with isomeric ketones by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and protic acids, respectively.^{2b} Interestingly, we noticed that bubbling dry HCl in a cooled (ca - 60 °C) solution of ketone β -1a in ether resulted in the formation of piperitenone 4 in high yield (81%).^{2c}



Given that sensitivity of β -1a to acidic conditions, the classical acetoxymercuration procedure was selected as a possible means to execute the planned hydration of this ketone. The usual conditions of such a process, which includes a treatment of an olefin by $\text{Hg}(\text{OAc})_2$ and the reduction of the resulting β -acetoxymercurinium species with alkaline sodium borohydride, appeared sufficiently mild to avoid a rearrangement of the pinenone system. However, submitting the ketone β -1a to these conditions did not furnish the expected hydration product 2a but instead, after dilution with water and acidification, an acidic compound (81%) which proved to be (NMR) a 85/15 mixture of, respectively, the carboxylic acid β -5a with its allylic isomer α -5a. Attractively, trituration of this mixture in hexane induced the crystallisation of the pure β -5a isomer (55%).³

Since the acid α -5a had been previously shown to form by treatment of ketone β -1a with aqueous bases, without specification of yield and selectivity however,^{2b} it was of interest to duplicate this experiment and to compare both the rate and the selectivity of such a base-induced rearrangement with those observed by using $\text{Hg}(\text{OAc})_2$. Accordingly, a solution of β -1a in methanolic KOH was refluxed for three hours. Partition of the resulting solution between water and ether and evaporation of the resulting organic phase afforded the ester 5b (17%; α -5b/ β -5b=89/11) whereas acidification of the aqueous extract resulted in the isolation of the acid 5a (63%; α -5a/ β -5a=87/13). Further treatment of the ester 5b by KOH/MeOH furnished additional acid 5a (same isomeric ratio), the pure acid α -5a being then isolated in fair yield (56%) by crystallization of the pooled acid fractions in hexane.

The opposite selectivity registered in, respectively, the mercuration and the basic conditions (Table), as well the harsh conditions required by using the latter, indicates clearly that two different pathways are involved.

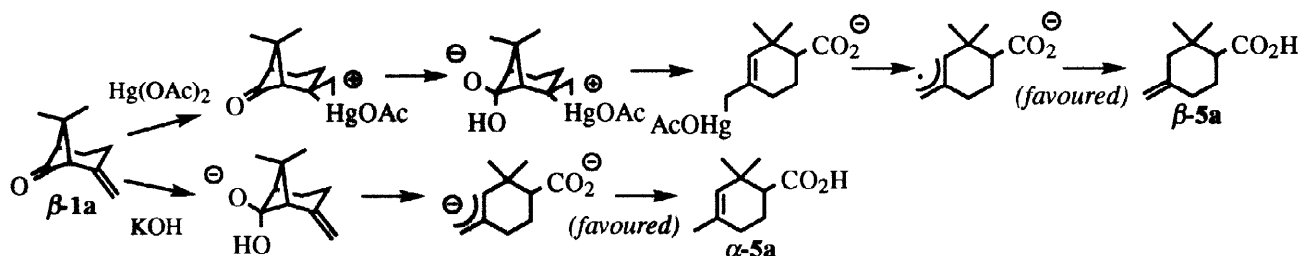


Reagents and conditions: 1- *i*) $\text{Hg}(\text{OAc})_2$ (1 eq.), 5/3 THF/ H_2O (4 ml/mmol); r. t., 30 s; *ii*) 3M NaOH (1.1 ml/mmol), then NaBH_4 (1 eq.), diluted with 3M NaOH (1.1 ml/mmol); r. t., 5 min.; 2- 2 M (in MeOH) KOH (2 ml/mmol); reflux, 3 hours; 3- Crystallization in hexane of the crude product from conditions 1; 4- Further treatment (ca 2 hours) by 2M (in MeOH) KOH of the ester fraction formed in conditions 2, then crystallization in hexane of the pooled acid fractions.

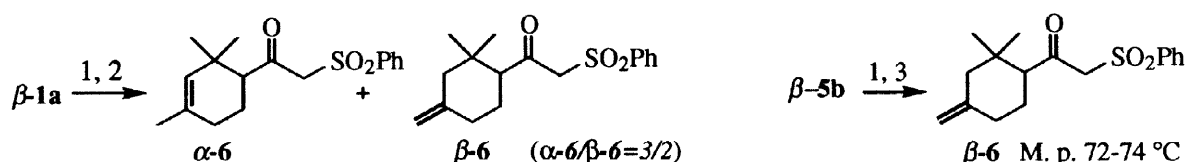
Table: Selectivity of the $\beta\text{-}1\text{a}$ -5 Conversion

Conditions	Composition of the Crude Reaction Mixture
1	$\alpha, \beta\text{-}5\text{a}$ (81%; $\alpha\text{-}5\text{a}/\beta\text{-}5\text{a}=15/85$)
2	$\alpha, \beta\text{-}5\text{a}$ (63%; $\alpha\text{-}5\text{a}/\beta\text{-}5\text{a}=87/13$), $\alpha, \beta\text{-}5\text{b}$ (17%; $\alpha\text{-}5\text{a}/\beta\text{-}5\text{b}=89/11$)

A rational might be that the initial electrophilic addition of a mercuric ion onto the carbon-carbon double bond of $\beta\text{-}1\text{a}$ by the less-hindered face generates the indicated mercurinium ion. Ensuing nucleophilic addition of an hydroxide anion onto the carbonyl group of this ion, followed by a Grob-like fragmentation, which should be strongly favoured on a stereoelectronic ground,⁴ will furnish an organomercuric species, whose subsequent reduction by a free-radical chain reaction, with preferential transfer of an hydrogen atom onto the more-substituted end (*i.e.* C-1) of the resulting allylic radical, will deliver the acid $\beta\text{-}5$, indeed the main product. Comparatively, fragmentation of the alkoxide species that would result from nucleophilic addition of an hydroxide ion onto the carbonyl group of $\beta\text{-}1\text{a}$ should be not so favoured. Additionally, protonation of the allylic carbanion thus released should occur preferentially at the less substituted end of the allylic system to give $\alpha\text{-}5\text{a}$, as observed.



Next, we attempted to condense the ketone $\beta\text{-}1\text{a}$ with the lithio derivative of methyl phenylsulfone with the hope that the alkoxide ion that should theoretically form would similarly fragment. This proved not so rewarding however, a 3/2 mixture (64%) of, respectively, the ketosulfone $\alpha\text{-}6$ and $\beta\text{-}6$ being isolated after an acidic work-up.⁵

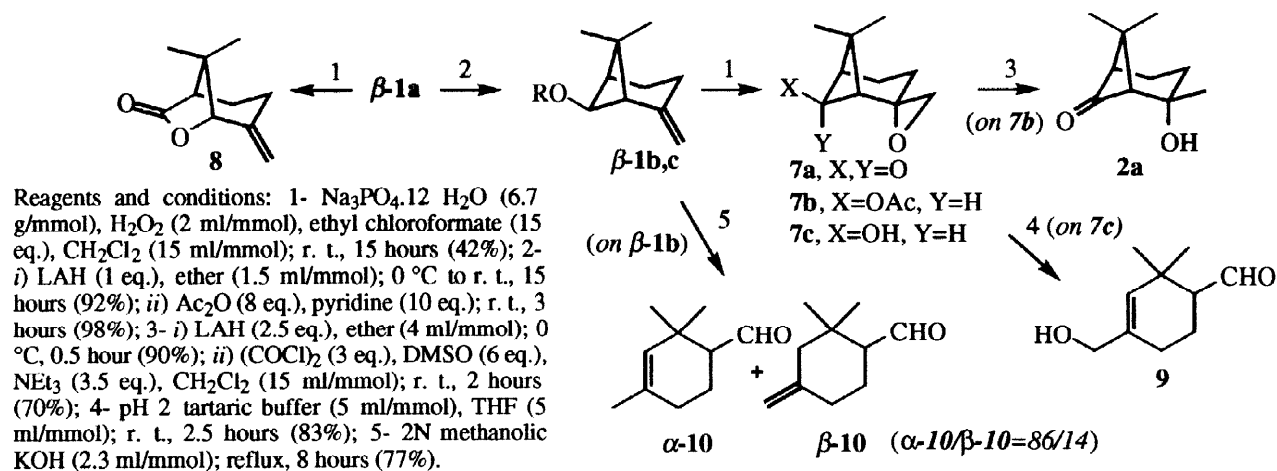


Reagents and conditions: 1- PhSO_2CH_3 (1.15 eq.), 1.55 M (in hexane) $n\text{-BuLi}$ (1.15 eq.), THF (2.6 ml/mmol); -78 $^{\circ}\text{C}$, 0.5 hour; 2- addition of $\beta\text{-}1\text{a}$ (1 eq.), diluted with THF (0.5 ml/mmol); -78 $^{\circ}\text{C}$ to 0 $^{\circ}\text{C}$, 6 hours, then AcOH; 3- addition of $\beta\text{-}5\text{b}$ (0.5 eq.), diluted with THF (0.5 ml/mmol); -78 $^{\circ}\text{C}$ to 0 $^{\circ}\text{C}$, 3 hours, then AcOH.

Obviously, this result was of limited synthetic interest, all the more since the pure ketosulfone $\beta\text{-}6$ could be obtained in fair yield (55%) by condensing excess methyl phenylsulfone with the ester $\beta\text{-}5\text{b}$.

Turning back our attention to our initial goal, we attempted next to prepare the ketoepoxyde **7a**, whose LAH reduction would have furnished the diol **2b**, potentially convertible into the target hydroxyketone **2a** by oxidation. Submitting β -**1a** to Bach epoxidation conditions,⁶ considered as the more appropriate to avoid a possible Baeyer-Villiger oxidation, resulted in the formation of the lactone **8**. That complication was surpassed by reducing β -**1a** into the known alcohol β -**1b**.^{2b} Acetylation of β -**1b** and treatment of the resulting acetate β -**1c** with ethyl chloroformate and hydrogen peroxide as precedently afforded the epoxy compound **7b**, then reduced into the diol **2b** by excess LAH. Finally, Swern oxidation of **2b** gave the target hydroxyketone **2a**.

Incidentally, we noticed that the use of aged (ca 3 months) LAH in the reduction step did not furnish the diol **2b** but instead the hydroxyepoxide **7c**, which rearranged partially into aldehydic compounds, as suggested by NMR, during an attempted purification by chromatography on silica gel. The slight acidity of the used support could be supposed to induce the observed degradation and indeed, treating the epoxide **7c** by a pH 2 tartaric buffer for a few hours resulted in the formation of the aldehyde **9** in good yield (83%). The ease with which that isomerisation took place lends credence to the scenario presented *vide supra* to explain the formation of the acid **5** by mercururation of pinenone β -**1a**. In the same mood, refluxing a solution of the alcohol β -**1b** in methanolic KOH resulted in the formation of a 86/14 mixture of, respectively, the aldehyde α -**10** and β -**10** in good yield (77%).⁷



In summary, the planned conversion of pinenone β -**1a** into the hydroxyketone **2a** proved difficult, being executed only by resort to a rather-long, stepwise, process. The observation during that endeavour of a few interesting rearrangements proved much rewarding however. The importance, especially in the preparation of carotenoids,⁸ of the compounds we thus obtained establishes the ketone β -**1a** as a valuable, pivotal, intermediate for synthesizing such terpenoids. Investigations along this line are being pursued.

Acknowledgements: Thanks are due to Rhône-Poulenc Industrialisation for a grant (to D. H.).

References and Notes

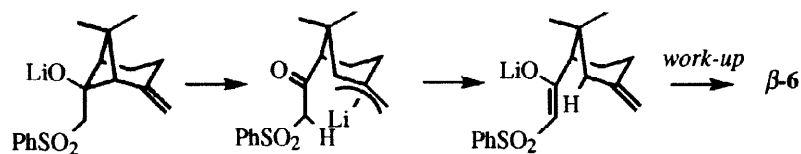
- 1- See the accompanying Letter.
- 2- a) Erman, W. F.; Wenkert, E.; Jeffs, P. W. *J. Org. Chem.* **1969**, *34*, 2196-2203, and references therein; b) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568-1576; c) Prepared from geranic acid according to ref. 2b. Purification of the crude product by column chromatography (silica gel; 9/1 hexane-AcOEt) proved necessary to eliminate the small amount of chrysanthenone α -**1** that also formed. Dry HCl was gently bubbled (1 bubble per sec.) for 5 minutes in a cooled (ca -60 °C) solution of β -**1a** (1 mmol) in dry ether (3 ml), after that the volatiles were removed *in vacuo* (oil pump), the temperature did not

exceeding 5 °C. Chromatography of the residue on silica gel (50/1 hexane/AcOEt) then afforded pure piperitenone **4** (121 mg; 81%); ^{13}C NMR: 22.6, 23, 23.9, 28, 32, 128.9, 129.1, 142.5, 159.7, 199.7; UV (MeOH): 243 (11,200), 277 (9,410) (Lit.:^{2d} 243 (12,600), 278 (7940); d) Naves, Y. R.; Conia, J.-M. *C. R. Acad. Sci. Ser. C* **1960**, 251, 1130.

3- β -**1a** (2 mmol), diluted with THF (2 ml), was added without cooling to a stirred solution of $\text{Hg}(\text{OAc})_2$ (2 mmol) in 1/1 THF/ H_2O (6 ml). 3M aqueous NaOH (2.2 ml) was subsequently added, with formation of an orange precipitate. A solution of NaBH_4 (1 eq.) in 3M NaOH (2.2 ml) was added rapidly and after 5 min. the resulting black-grey mixture was filtered on Celite. The solids were washed with water (100 ml) and the pooled filtrates were washed with ether (3x50 ml), acidified to pH 2 with 10N HCl (1 ml), then extracted with ether (3x50 ml). That last organic phase was washed with brine (3x50 ml), dried (MgSO_4) and evaporated to leave an oil (222 mg) which was filtered on silica gel (hexane/AcOEt). Evaporation of the solvents, then crystallization of the residual oil in hexane afforded the acid β -**5a** (183 mg; 55%); M. p. 65-67 °C; anal.: C 71.23 (calc. 71.39), H 9.74 (calc. 9.59); ^1H NMR: 0.93 (s, 3H), 1.08 (s, 3H), 1.63-2.08 (m, 5H), 2.29-2.42 (m, 2H), 4.61 (d (A part of an AB system), $J_{\text{AB}}=2.4$ Hz, $\Delta\nu=22.5$ Hz, 1H), 4.72 (d (B part of an AB system), $J_{\text{AB}}=2.4$ Hz, $\Delta\nu=22.5$ Hz, 1H); ^{13}C NMR: 21.5, 26, 30, 33.3, 34.7, 49.4, 52, 109.6, 145.5, 184.4.

4- Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, 25, 4455-4458.

5- This poor selectivity, as compared to that registered in the KOH-induced cleavage of β -**1a**, could result from a possible competition between *intramolecular* and *intermolecular* protonation of the formed allylic anion by the acidic ketosulfone residue. The former process, leading preferentially, as shown, to the β -**6** isomer, should be favoured by lowering the reagent concentration. Indeed, the α -**6**/ β -**6** ratio dropped to 2/3 by adding slowly β -**1a** to a diluted solution of the lithiosulfone in THF.



6- Bach, R. D.; Klein, M. J.; Ryntz, R. A.; Holubka, J. W. *J. Org. Chem.* **1979**, 44, 2569-2571.

7- Selected data: α -**5a**: ^{13}C NMR: 22.3, 23.5, 24.6, 29.3, 30.1, 34.4, 50.1, 131.2, 131.9, 181.3; β -**6**: m. p. 71-72 °C; anal.: C 66.83 (calc. 66.64), H 7.02 (calc. 7.24); ^1H NMR: 0.8 (s, 3H), 1 (s, 3H), 1.58-1.79 (m, 2H), 1.93-2.08 (m, 3H), 2.29 (dt, $J=13.6$, 4.3 Hz, 1H), 2.81 (dd, $J=10.4$, 4.2 Hz, 1H), 4.13 (d (A part of an AB system), $J_{\text{AB}}=13.4$ Hz, $\Delta\nu=29.2$ Hz, 1H system), 4.29 (d (A part of an AB system), $J_{\text{AB}}=13.4$ Hz, $\Delta\nu=29.2$ Hz), 4.59 (m, 1H), 4.71 (m, 1H), 7.53-7.72 (m, 3H), 7.87-7.91 (m, 2H), ^{13}C NMR: 21.3, 25.4, 30, 33.2, 35.7, 49.3, 59.3, 68.3, 109.9, 128.5, 129.4, 134.3, 138.9, 145, 201.3; **8**: ^1H NMR: 0.95 (s, 3H), 1.16 (s, 3H), 1.75-1.86 (m, 2H), 2.23-2.38 (m, 3H), 4.38 (s, 1H), 4.88 (s, 1H), 4.9 (s, 1H); ^{13}C NMR: 19.3, 21.6, 25.5, 25.9, 41.8, 48.9, 90.4, 112.4, 141.8, 179; β -**1c**: Bp_{0.8} 75 °C; ^1H NMR: 0.77 (s, 3H), 1.4 (s, 3H), 1.59-2.32 (m, 4H), 2.09 (s, 3H), 2.41-2.5 (m, 1H), 2.61 (d, $J=6.2$ Hz, 1H), 4.56-4.7 (m, 3H); ^{13}C NMR: 21.4, 23.4, 23.5, 23.7, 27.5, 40, 45.2, 56, 77.3, 107.9, 149.4, 170.3; **7b**: ^1H NMR: 0.94 (s, 3H), 1.38 (s, 3H), 1.68-2.11 (m, 6H), 2.04 (s, 3H), 2.59 (d (A part of an AB system), $J_{\text{AB}}=4.8$ Hz, $\Delta\nu=27.2$ Hz, 1H), d (B part of an AB system), $J_{\text{AB}}=4.8$ Hz, $\Delta\nu=27.2$ Hz, 1H); ^{13}C NMR: 21.4, 22.6, 22.7, 23.9, 27.6, 40, 45.5, 52.9, 61.7, 75.6, 170.4; **7c**: ^1H NMR: 0.96 (s, 3H), 1.53 (s, 3H), 1.55-2.05 (m, 5H), 2.3 (d, $J=2.5$ Hz, 1H), 2.64 (d (A part of an AB system), $J_{\text{AB}}=2.6$ Hz, $\Delta\nu=25$ Hz, 1H), 2.76 (d (B part of an AB system), $J_{\text{AB}}=2.6$ Hz, $\Delta\nu=25$ Hz, 1H), 4.34 (d, $J=2.6$ Hz, 1H); ^{13}C NMR: 22.9, 23.2, 24.1, 28.3, 39.9, 46.2, 54.9, 56.3, 62.8, 73.1; **2b**: m.p. 145-146 °C; anal.: C 70.42 (calc. 70.55), H 10.55 (calc. 10.66); ^1H NMR: 0.97 (s, 3H), 1.35 (s, 3H), 1.39 (m, 1H, OH), 1.53 (s, 3H), 1.7-1.97 (m, 6H), 4.22 (s, 1H); ^{13}C NMR (d^6 -acetone): 26, 26.8, 29.8, 31.9, 33.1, 37.8, 47.9, 61.4, 75.6, 76.6; **2a**: m.p. 42-44 °C; anal.: C 71.57 (calc. 71.4), H 9.48 (calc. 9.59); ^1H NMR: 1.17 (s, 3H), 1.3 (s, 3H), 1.36 (s, 3H), 1.74 (m, 1H), 1.95 (m, 1H), 2.02-2.29 (m, 2H), 2.52-2.59 (m, 3H); ^{13}C NMR: 18.6, 26.5, 29.8, 31.1, 31.2, 31.6, 63, 75.3, 81.5, 212.7; **9**: ^1H NMR: 1.01 (s, 3H), 1.23 (s, 3H), 1.71-2.03 (m, 5H), 2.22 (ddd, $J=11.1$, 2.6, 2.5 Hz, 1H), 4 (m, 2H), 5.37 (s, 1H), 9.86 (d, $J=2.3$ Hz, 1H); ^{13}C NMR: 19.45, 24.5, 24.6, 29.7, 34, 56.4, 66.7, 132.6, 135.2, 203.7. Excepted when otherwise stated: ^1H and ^{13}C NMR at 200 and 50 MHz, in CDCl_3 .

8- See, for instance: Férézou, J.-P.; Julia, M. *Tetrahedron* **1990**, 46, 475-486, and quoted references.