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AN EFFICIENT SYNTHESIS OF JUVABIONE AND TODOMATUIC ACID VIA HYDROBORATION-CARBONYLATION

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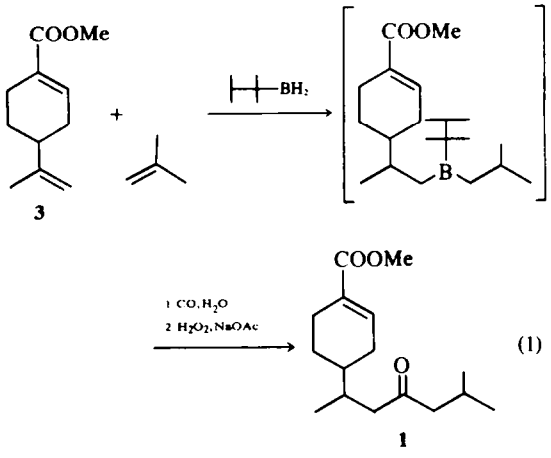
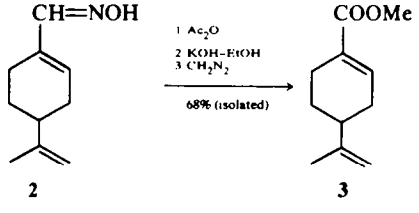
Abstract—An efficient synthesis of juvabione (**1a**) and todomatuic acid (**4**), the key step of which involves a one-step conversion of methyl perillate (**3**) to a mixture consisting of **1a** and epijuvabione (**1b**) via hydroboration-carbonylation is reported.

JUVABIONE[1] has drawn considerable attention in recent years because of its high juvenile hormone activity. Although several syntheses have been reported, they require a number of steps, producing juvabione (**1a**) in low overall yields. Simple retrosynthetic considerations suggested that the multi-carbon–carbon bond formation via "stitching" by hydroboration[2] and "rivetting" by carbonylation[3] might be applicable to an efficient construction of the required skeleton (Eqn 1). We were further attracted by the commercial availability of perillartine[4] (**2**) which could readily be converted to the required intermediate **3**.



(1)

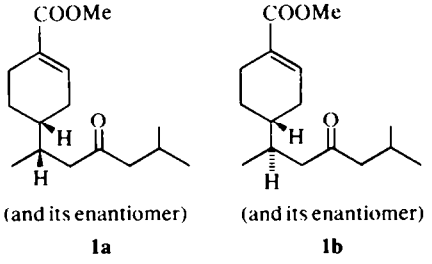
Conversion of **2** into **3**, indeed, proved to be straightforward and was carried out in a manner similar to that reported previously[5] (Eqn 2).

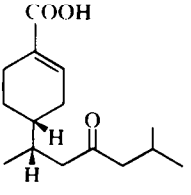


(2)

Methyl perillate (**3**) was reacted at −25° in the presence of 0·5 equiv of 2,3-dimethyl-2-butene with thexylisobutylborane prepared by a successive hydroboration of 1 equiv each of 2,3-dimethyl-2-butene (0°, 1 hr) and isobutylene (−25° 1 hr) with borane in tetrahydrofuran (THF).[6] Without isolation the mixture was carbonylated[5] at 70 atm and at 50° after addition of 2 equiv of water. Oxidation of the carbonylation mixture with hydrogen peroxide and sodium acetate[7] followed by distillation afforded a product exhibiting a single GLC peak (>99% on columns packed with SE-30 and Carbowax 20 M) in 78% yield by isolation based on **3** (or 53% based on **2**), b.p. 128–131° (0·04 mm).

The product thus isolated proved to be a nearly 1:1 mixture of juvabione (**1a**) and epijuvabione (**1b**) as judged by the ^{13}C NMR spectrum.





The methyl and methylene carbon atoms adjacent to the acyclic asymmetric C atom exhibit closely appearing doublets at 16·42 and 16·52, and 47·79 and 47·91 ppm (relative to TMS), respectively. Several other C atoms including the two asymmetric methine C atoms also exhibit doublets. Making reasonable assumptions that the relaxation times (T_1) and the NOE factors for the corresponding C atoms are nearly equal, we estimate that the product consists of 50 ± 5% each of **1a** and **1b**. Our attempts to observe them separately by GLC, high pressure LC or ^1H NMR have been unsuccessful.

Conversion of the mixture of **1a** and **1b** into todomatuic

acid (4) was carried out on a small scale as reported earlier[1b,1d] by a sequence consisting of alkaline hydrolysis, formation and separation by recrystallization of epimeric semicarbazones of the keto acids, and acidic hydrolysis of the crystalline semicarbazone of 4. The epimerically pure 4 was converted to 1a by treating 4 with diazomethane. Both todomatuic acid (4) m.p. 64–65° (lit.[1b] m.p. 66–67°), and juvabione (1a) n^{20}D 1·4818 (lit.[1b] n^{19}D 1·4818) thus obtained were identical in all respects with their authentic samples.

Although non-stereoselective, the synthesis reported here provides a highly efficient, regio- and chemoselective[8] construction of the juvabione skeleton, which does not require the usual protection-deprotection of carbonyl functional groups, thus pointing to certain unique advantages associated with the electrophilic nature of organoboranes.

EXPERIMENTAL

1-Cyano-4-isopropenyl-1-cyclohexene (perillonitrile).[5a] To 16·5 g (100 mmol) of perillartine placed in a 300-ml flask fitted with a reflux condenser and a magnetic stirring bar was added 100 ml Ac_2O. After refluxing overnight, 2 × 100 ml pentane was added to the mixture. The organic layer was washed with water, sat. $NaHCO_3$aq and water; it was then dried over $MgSO_4$. Distillation provided 12·9 g (88%) of the title substance, b.p. 65–66° (0·5 mm); $n^{20.5}$D 1·4960; >99% pure by GLC; ^{1}H NMR (CCl_4, TMS) δ 1·2–2·6 (m with peaks at 1·77 and 2·2–2·4, 10H), 4·7–4·9 (m, 2H) and 6·5–6·7 (m, 1H) ppm; IR (neat) 2220(s), 1640(s), 1450(s), 1430(s), 895(s), 840(s) cm^{-1}.

Perillic acid.[5a] To 7·4 g (50 mmol) 1-cyano-4-isopropenyl-1-cyclohexene and 10 ml EtOH placed in a 300 ml flask with a magnetic stirring bar and a reflux condenser was added 20% KOH aq (100 ml). After refluxing for 12 hr, the mixture was cooled in an ice bath and 6 N HCl was added to pH *ca.* 2. The ppt was filtered off, washed with water (3 × 100 ml) and dried *in vacuo*. The crude acid (m.p. 123–125°) was obtained in 96% yield (7·96 g), which was used without further purification for esterification. A sample of the crude product was recrystallized from EtOH, m.p. 130–131° (lit.[5a] m.p. 130–131°[c]).

Methyl perillate[5b] (3). Perillic acid (7·76 g, 46·74 mmol) was dissolved in 50 ml ethyl ether, and a 0·41 M soln of diazomethane in ether (114 ml) was slowly added at 0°. The mixture was stirred for an additional hr at 0° and the ether removed under reduced pressure. The residue was distilled to give 6·73 g (37·4 mmol, 80%) of methyl perillate; b.p. 81–83° (0·5 mm) [lit.[5b] b.p. 81°[c] (0·28 mm)]; ^{1}H NMR (CCl_4, TMS) δ 1·73 (m, 3H), 2·0–2·6 (m, 7H), 3·66 (s, 3H), 4·73 (m, 2H), and 6·8–7·1 (m, 1H) ppm; IR (neat) 1720(s), 1650(s) cm^{-1}.

Conversion of methyl perillate (3) into a mixture consisting of juvabione (1a) and epijuvabione (1b). To 12·0 ml (30 mmol) of 2·50 M borane in THF in a 200-ml flask equipped with a septum inlet, a magnetic stirring bar, and an outlet connected to a mercury bubbler were added sequentially 2·52 g (30 mmol) of 2,3-dimethyl-2-butene (0°, hr), 1·68 g (30 mmol) of isobutylene (−25°, 1 hr), 1·26 g 15 mmol) of 2,3-dimethyl-2-butene (−25°, 5 min), 5·40 g (30 mmol) of methyl perillate (−25°, several hr), and 1·08 ml (60 mmol) of water. The resultant mixture was transferred to a 250-ml autoclave using *ca.* 25 ml of THF for a complete transfer of the mixture and carbonylated overnight with CO at 70 atm and 50°. The carbonylated mixture was oxidized in the original flask using 15 ml each of 3 N NaOAc and 30% H_2O_2 at 30–40°. After heating the mixture at 50° for 1 hr, extraction with ether, drying over $MgSO_4$ and fractional distillation provided 6·2 g (78%) of a nearly 1:1 mixture of 1a and 1b, b.p. 128–131°[c] (0·04 mm); ^{1}H NMR ($CDCl_3$, TMS) δ 0·88 (d, J = 6 Hz, 3H) 0·91 (d, J = 6 Hz), 6H), 1·2–2·6 (m, 13H), 3·72 (s, 3H) and 6·9–7·1 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 16·43, 16·52, 22·57,[9] 24·79, 24·94, 26·14, 28·52, 29·74, 32·66, 32·90, 37·74,[9] 47·79, 47·91, 51·40, 52·44,[9] 130·25, 139·18, 167·73 and 210·33 ppm; IR (neat) 1720(s), 1650(w), 1250(s), 1082(m) cm^{-1}.

Todomatuic acid (4). Hydrolysis of the mixture of 1a and 1b (1·32 g, 8·0 mmol) was carried out with 40 ml each of 1 N KOH and MeOH as reported previously.[1d] The crystalline product obtained after the work-up[1d] weighed 1·06 g (87%); m.p. 52–53°. The semicarbazones of todomatuic acid and its stereoisomer were prepared as reported previously[1b] by treating 0·608 g (4·0 mmol) of the product obtained above with semicarbazide hydrochloride and NaOAc. The crystalline semicarbazone obtained after recrystallization (EtOH) weighed 0·352 g (42%); m.p. 185–187° (lit.[1b] m.p. 186–188°). The crystalline semicarbazone (0·209 g, 1 mmol) was converted to todomatuic acid (4) as reported previously[1b] by hydrolysis with H_2SO_4. There was obtained 0·117 g (77%) of 4, m.p. 64–65°[c] (lit.[1b] m.p. 66–67°); ^{1}H NMR (CCl_4, TMS) δ 0·83 (d, J = 6 Hz, 3H), 0·87 (d, J = 6 Hz, 6H), 1·2–2·6 (m, 13H), 6·9–7·2 (m, 1H), and 10·5 (s, 1H) ppm; IR (CCl_4) 1710(s), 1690(s), 1650(m), 1270(s) cm^{-1}.

Juvabione (1a). Todomatuic acid 4 (76 mg, 0·5 mmol) was esterified with diazomethane and purified by column chromatography to produce 79 mg (95%) of juvabione, n^{20}D 1·4818 (lit.[1b] n^{19}D 1·4818). Its ^{1}H NMR and IR spectra are virtually indistinguishable from those of the mixture of 1a and 1b obtained earlier.

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REFERENCES

[1a] W. S. Bowers, H. M. Fales, M. J. Thompson and E. C. Uebel, *Science* **154**, 1020 (1966); [b] K. Mori and M. Matsui, *Tetrahedron* **24**, 3127 (1968); [c] K. S. Ayyar and G. S. K. Rao, *Can. J. Chem.* **46**, 1467 (1968); [d] B. A. Pawson, H. C. Cheung, S. Gurbaxani and G. Saucy, *J. Am. Chem. Soc.* **92**, 336 (1970); [e] A. J. Birch, P. L. Macdonald and V. H. Powell, *J. Chem. Soc.* C, 1469 (1970); [f] J. Ficini, J. D'Angelo and J. Noire, *J. Am. Chem. Soc.* **96**, 1213 (1974).

[2a] H. C. Brown, *Hydroboration.* Benjamin, New York, 1962; [b] H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, New York (1972).

[3a] H. C. Brown, *Accounts Chem. Res.* **2**, 65 (1969); [b] E. Negishi, *Intra. Sc. Chem. Rept.* **7**, 81 (1973).

[4] Obtained from Aldrich Chemicals, Inc. The sample used in the present study was essentially racemic. Use of perillaldehyde as a starting material for 1a has been suggested.[1d]

[5a] For the conversion of 2 into perillic acid, see J. J. Ritter and D. Ginsburg, *J. Am. Chem. Soc.* **72**, 2381 (1950); [b] For the conversion of perillic acid into 3, see A. C. Hortmann and A. Q. Ong, *J. Org. Chem.* **35**, 4291 (1970).

[6a] E. Negishi and H. C. Brown, *Synthesis* 77 (1974); [b] H. C. Brown, E. Negishi, and J. J. Katz, *J. Am. Chem. Soc.* **97**, 2791 (1975); H. C. Brown, J. J. Katz, C. F. Lane and E. Negishi, *Ibid.* **97**, 2799 (1975).

[7] Use of stronger bases, such as sodium hydroxide, must be avoided. For related procedures, see [a] H. C. Brown and E. Negishi, *J. Am. Chem. Soc.* **89**, 5285 (1967); [b] E. Negishi and H. C. Brown, *Synthesis* **196** (1972).

[8] Chemical transformations without the protection of other functional groups may conveniently be classified as being chemoselective or chemospecific. *cf* B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.* **95**, 6840 (1973).

[9] These peaks are partially split doublets.