Stereocontrolled Synthesis of (±)-Coryantheidol from (±)-Norcamphor

By Seiichi Takano,* Ken'ichi Masuda, and Kunio Ogasawara

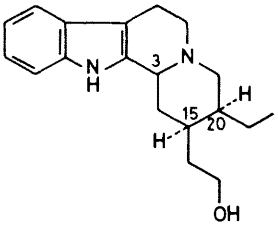
(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*)

Summary A highly stereoselective synthesis of (±)-corynantheidol (**1**) has been carried out using (±)-norcamphor (**3**) as a starting material.

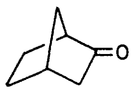
Recently we have shown norcamphor (**3**) to be an excellent building block for the construction of the non-amine unit of the ipecac[1] and the yohimbinoid[2] alkaloids. We now report an additional application in a highly stereoselective synthesis of (±)-corynantheidol[3] (**1**) with the less stable *cis* C(15)/C(20) configuration.

Treatment of the bicyclic lactone[1a] (**4**), obtained stereoselectively in 51% overall yield from (±)-norcamphor (**3**), with benzylamine at 180—200 °C afforded the amide (**5**),† m.p 130—132 °C, in 73% yield, which on Jones oxidation yielded the ketone (**6**), m.p. 103—104 °C, in 73% yield. Regioselective thioacetalization by treatment of the pyrrolidine enamine derived from (**6**) with trimethylene dithiotosylate[4] in the presence of triethylamine gave the α-diketone monothioacetal (**7**), m.p. 144—146 °C, which was cleaved with KOH in Bu^tOH[5] to give the carboxylic acid (**8**), m.p. 132—134 °C, in 64% overall yield from (**6**). Reduction of the carboxy group of (**8**), *via* the mixed anhydride with ethyl chloroformate,[6] afforded the primary alcohol (**9**) as an oil in 84% yield. Heating (**9**) in diphenylmethane at 200 °C for 24 h furnished the oily δ-lactone (**10**) with the *cis* C(1)/C(2) configuration in 64% yield.‡ Treatment of (**10**) with $KOBu^t$ in tetrahydrofuran (THF) at room temperature brought about smooth epimerization at the C(1) centre *via* the enolate (**11**) to allow almost quantitative conversion into the epimeric δ-lactone (**12**) with the *trans* C(1)/C(2) configuration.

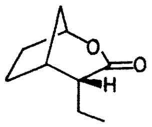
Reduction of (**12**) with di-isobutylaluminium hydride in toluene at −25 °C afforded an epimeric mixture of the lactols (**13**) which, without purification, was condensed with tryptamine in refluxing MeOH, followed by reduction with $NaBH_4$ in the same flask to furnish the amino-alcohol (**14**) as an oil, in 83% overall yield from (**12**).



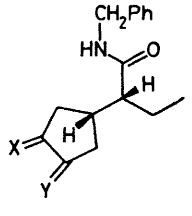
(**1**) Corynantheidol (3Hα)
(**2**) Epicorynantheidol (3Hβ)



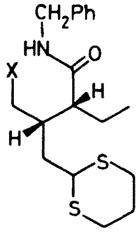
(**3**)



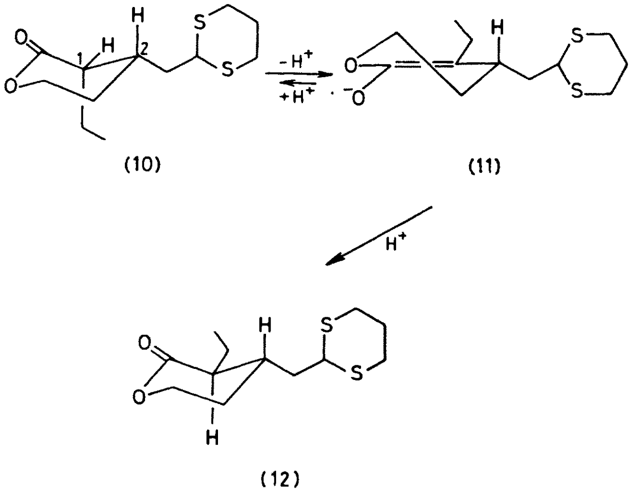
(**4**)



(**5**) X = OH, H; Y = H_2
(**6**) X = O; Y = H_2
(**7**) X = O; Y = $-S[CH_2]_3S-$



(**8**) X = CO_2H
(**9**) X = CH_2OH

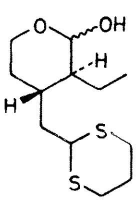


(**10**) (**11**) (**12**)

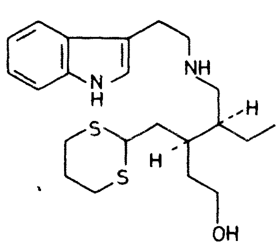
---

† Satisfactory analytical and spectral data were obtained for all new compounds.

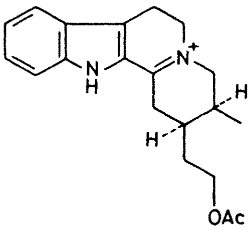
‡ At this stage, the thermodynamic formation of the *trans* isomer (**12**) was clearly observed by t.l.c.



(13)



(14)



(15)

Upon hydrolysis of the dithian group with methyl iodide in aqueous MeCN,[7] the hydrochloride of (**14**) afforded (±)-corynantheidol (**1**), m p 157—159 °C (lit ,[3] 158—162 °C) and (±)-3-epicorynantheidol (**2**), m p 192—194 °C (lit ,[3] 191—192 °C), in yields of 8 and 63% through a concurrent Pictet–Spengler-type cyclization[8] without causing quaternization of the tertiary nitrogen [9] The latter, after acetylation, was dehydrogenated with mercuric acetate[1a,10,11] to give the iminium base (**15**) which on reduction with $NaBH_4$,[1a,3] followed by alkaline hydrolysis furnished the former (**1**) in 56% overall yield On similar treatment, the former regenerated (±)-corynantheidol (**1**) in comparable yield through (**15**) [11] These conversions indicated that these compounds were the C(3) epimers of each other and moreover, the presence of the Bohlmann bands in the i r spectrum of each indicated both to have the *cis* C(15)/C(20) configuration [10] Since chiral norcamphor has been obtained,[12] the present method would be applicable to a chiral synthesis of the related alkaloids

(*Received*, 10*th June* 1980, *Com.* 631)

---

[1] (a) S Takano, S Hatakeyama, and K Ogasawara, *Tetrahedron Lett* , 1978, 2519, (b) S Takano, Y Takahashi, S Hatakeyama, and K Ogasawara, *Heterocycles*, 1979, **12**, 765

[2] (a) S Takano, M Takahashi, S Hatakeyama, and K Ogasawara, *J Chem Soc* , *Chem Commun* , 1979, 556, (b) S Takano, M Takahashi, and K Ogasawara, *J Am Chem Soc* , 1980, **102**, 4282

[3] For an alternative stereoselective synthesis see E Wenkert, K G Dave, and F Haglid, *J Am Chem Soc* , 1965, **87**, 5461

[4] R B Woodward, I J Pachter, and M L Scheinbaum, *Org Synth* , 1974, **54**, 33,39

[5] *Cf* J A Marshall and D E Seitz, *J Org Chem* , 1974, **39**, 1814

[6] *Cf* K Ishizumi, K Koga, and S Yamada, *Chem Pharm Bull* , 1968, **16**, 492

[7] M Fetizon and M Jurion, *J Chem Soc* , *Chem Commun* , 1972, 382

[8] S Takano, S Hatakeyama, and K Ogasawara, *J Am Chem Soc* , 1976, **98**, 3022, 1979, **101**, 6414

[9] *Cf* S Takano, S Hatakeyama, and K Ogasawara, *J Chem Soc* , *Perkin Trans* 1, 1980, 457

[10] N J Dastoor, A A Gorman, and J Schmid, *Helv Chim Acta*, 1967, **50**, 213

[11] H T Openshaw and N Whittaker, *J Chem Soc* , 1963, 1461

[12] H C Brown, N R Ayyanger, and G Zweifel, *J Am Chem Soc* , 1964, **86** 397, R K Hill and A G Edwards *Tetrahedron*, 1965, **21**, 1501, R N McDonald and R N Steppel, *J Am Chem Soc* , 1969, **91**, 782, S Takano, H Iwata and K Ogasawara, *Heterocycles*, 1978, **9**, 845

Printed by Heffers Printers Ltd Cambridge England