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References and Notes

1) M.S.F. Ross, *J. Chromatogr.*, **141**, 107 (1977), and references quoted therein.
2) T. Kawasaki, M. Maeda, and A. Tsuji, *J. Chromatogr.*, **163**, 143 (1979).
3) N. Nimura and T. Kinoshita, *Anal. Lett.*, **13**, 191 (1980).
4) J. Goto, N. Goto, A. Hikichi, T. Nishimaki, and T. Nambara, *Anal. Chim. Acta*, **120**, 187 (1980).
5) K.E. Koenig and W.P. Weber, *Tetrahedron Lett.*, **1974**, 2275.
6) A. Fischer, H.M. Fountain, and J. Vaughan, *J. Chem. Soc.*, **1959**, 1310.
7) J. Goto, H. Kato, F. Hasegawa, and T. Nambara, *Chem. Pharm. Bull.*, **27**, 1402 (1979).

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1,6-Dihydro-3(2*H*)-pyridinones as Synthetic Intermediates. A Convenient Total Synthesis of (±)-Cleavamine

A novel and convenient total synthesis of (±)-cleavamine (**1**) starting from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**2**) is described.

Keywords——total synthesis; cleavamine; Claisen rearrangement; 1,3-diaxial interaction; medium-ring closure

The cleavamine-type compounds are of particular interest in that they constitute the indole portion of the bis indole-dihydroindole alkaloids represented by vinblastine, one of clinically important antitumor agents, and that they have provided key intermediates for pentacyclic *Iboga* alkaloids.[1] Therefore, it is of great value to develop convenient synthetic methods for cleavamine and related compounds, and a number of synthetic studies on the cleavamine family, *e.g.* cleavamine or velbanamine, have been reported to data.[2] Now we wish to report here a novel and convenient total synthesis of (±)-cleavamine (**1**) from an easily available starting material, ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate[3] (**2**), which has been shown to be a common synthon for various alkaloids.[4]

The allylic alcohol (**3**), obtained in 52% yield by the reaction of **2** with ethylmagnesium bromide,[4b] was heated in ethyl vinyl ether containing mercuric acetate at 200° for 72 hr to provide the aldehyde (**4**). Its ethylene acetal (**5**; 66% yield from **3**) was hydrolyzed with potassium hydroxide in aqueous ethanol to give the amine (**6**) [59%,[5] δ: 0.98 (3H, t, J=7), 1.65 (2H, d-d, J=6, 4.5), 1.90 (2H, q, J=7), 2.02 (1H, s), 3.15 (2H, m), 3.83 (4H, m), 4.84 (1H, t, J=4.5), 5.33 (1H, m)]. Condensation of **6** with β-indolylacetyl chloride in methylene chloride afforded the amide (**7**) quantitatively, an acidic hydrolysis of which gave the aldehyde (**8**). On oxidation with silver(I) oxide the aldehyde (**8**) was converted smoothly to the carboxylic acid (**9**) in 67% yield from **7**. Cyclization of **9** to the dioxocleavamine (**10**) [36%, mp 199—200°, *m/e*: 308 (M^+), ν: 3470, 1650, δ: 1.02 (3H, t, J=7), 1.98 (2H, q, J=7), 3.39 (1H,

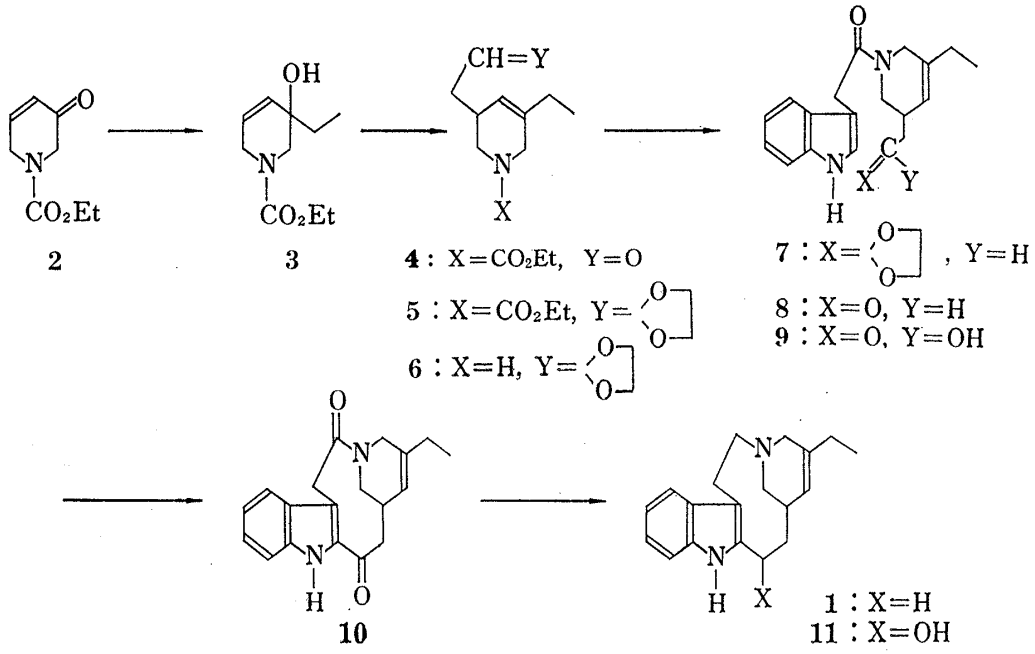

Chart 1

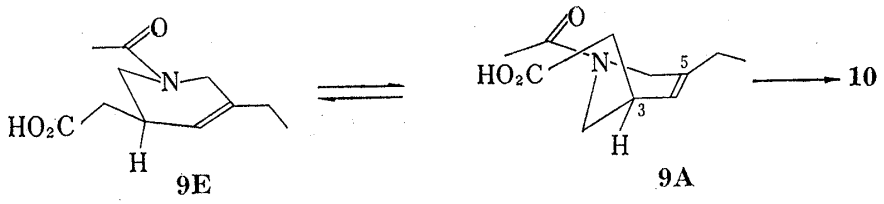

Chart 2

d, J=17), 4.25 (2H, s), 4.85 (1H, d, J=17), 5.58 (1H, m), 6.90—7.38 (3H, m), 7.65 (1H, m), 9.09 (1H, m)] was effected by the action of polyphosphate ester[6] in chloroform under reflux for 2 hr.[7] The successful cyclization could be interpreted by the fairly high contribution of the requisite C_3-axial conformation (**9A**) due to the sp^2 character at C_5.[8] Finally, lithium aluminum hydride reduction of **10** in dioxane furnished (±)-cleavamine (**1**) [13%, mp 113—114.5°, *m/e*: 280 (M^+), λ (MeOH) 229.5 (4.40), 285.5 (3.76), 292.5 (3.72), ν 3450, 1620, δ: 1.06 (3H, t, J=7), 2.00 (2H, q, J=7), 5.25 (1H, m), 6.88—7.32 (3H, m), 7.42 (1H, m), 7.72 (1H, s)] along with the hydroxycleavamine (**11**, 42%, mp 173—174°).[9] The synthetic (±)-cleavamine was proved to be identical with (+)-cleavamine in UV, IR, and PMR spectra. Thus, a novel synthesis of (±)-cleavamine was completed and further the dioxo- or hydroxycleavamine easily obtained by the present investigation would be utilized as a potential synthetic intermediate for other cleavamine type compounds.

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References and Notes

1) *cf.* J.P. Kutney, W.J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *J. Am. Chem. Soc.*, **88**, 4756 (1966); *idem*, *ibid.*, **92**, 1712 (1970).
2) S. Takano and K. Ogasawara, *Yuki Gosei Kagaku Kyokai Shi*, **35**, 795 (1977) and references cited therein; J. Harley-Mason and Atta-ur-Rahman, *Tetrahedron*, **36**, 1057 (1980); Atta-ur-Rahman, J.A. Beisler, and J. Harley-Mason, *ibid.*, **36**, 1063 (1980); S. Takano, C. Murakata, and K. Ogasawara, *Heterocycles*, **14**, 1301 (1980).

3) T. Imanishi, I. Imanishi, and T. Momose, *Syn. Commun.*, **8**, 99 (1978).
4) *a*) T. Imanishi, H. Shin, M. Hanaoka, T. Momose, I. Imanishi, *Heterocycles*, **14**, 1111 (1980); *b*) T. Imanishi, H. Shin, N. Yagi, and M. Hanaoka, *Tetrahedron Lett.*, **21**, 3285 (1980); *c*) T. Imanishi, N. Yagi, and M. Hanaoka, *ibid.*, **22**, 667 (1981).
5) 92% yield on the basis of the consumed starting material.
6) W. Pollmann and G. Schramm, *Biochim. Biophys. Acta*, **80**, 1 (1964).
7) The same cyclization using polyphosphoric acid (PPA) gave **10** in a rather low yield (12%).
8) A similar carboxylic acid bearing sp^3 carbon at the 5-position was found to give only polymeric product by cyclization using PPA. See, F.E. Ziegler, J.A. Kloek, and P.A. Zoretic, *J. Am. Chem. Soc.*, **91**, 2342 (1969).
9) The results were obtained from the reduction for 2 hr, and that for a longer time (3 hr) afforded **1** and **11** in 19 and 24% yield, respectively.

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Synthesis of 28-Norbrassinolide[1)]

28-Norbrassinolide (2α,3α,22*R*,23*R*-tetrahydroxy-B-homo-7-oxa-5α-cholestan-6-one), which is an analog of the plant growth promoting steroidal lactone, brassinolide, was synthesized *via* 22*R*,23*R*-dihydroxycholesterol. Syntheses of the other C-22, 23 stereoisomers of 22,23-dihydroxycholesterol were also described.

Keywords——brassinolide; plant growth promoter; 22,23-dihydroxycholesterol; 22-dehydrocholesterol; Baeyer–Villiger oxidation

Brassinolide (**1**) isolated from rape pollen is a steroidal lactone producing a novel plant growth-promoting effect.[2)] The remarkable biological activity[2,3)] and the novel structural features made **1** an enticing synthetic target. We[4)] and others[5)] have recently completed synthesis of **1**. Syntheses of the analogs, 24-epibrassinolide **2**[6)] and homo-brassinolide **3**[7)] were also reported. It is interesting to note that **2** and **3** showed potent but a little weaker biological activity, compared to **1**.[3,6)] To have a further insight into the C-24 substituent effect on biological activity and the stereochemical importance of the vicinal glycol moiety, we have now aimed to synthesize all the four C-22, 23 stereoisomers of 28-nor-brassinolide. Described here are syntheses of the synthetic progenitors, 22,23-dihydroxycholesterols (**6**—**9**) and transformation of one of the stereoisomers **6** into 28-norbrassinolide (**20**).

Apparently, the precursors of the vicinal glycols (**6**—**9**) are (22*E*)- and (22*Z*)-dehydrocholesterol (**4** and **5**). The *Z* olefin **5**, mp 137—139°, was easily prepared according to the published method.[8)] The *E* isomer **4**, mp 130—132°, was obtained in 68% overall yield from the previously described[9)] ester **14** in four steps: (i) LAH/THF; (ii) MsCl/pyridine; (iii) LAH/THF; (iv) a trace of HCl–MeOH. Oxidation of the *E* olefin **4** with a catalytic amount of OsO_4 and N-methylmorpholine N-oxide in *t*BuOH–THF–H_2O (10: 6: 1)[10)] gave a mixture (75% yield) of the more polar triol **6**, mp 187—191°, and the less polar triol **7**, mp 182—183° (2: 5). Since the *Z* olefin **5** was more reluctant to react in the same conditions, this was treated with OsO_4 in Et_2O for 10 days to give a mixture (69% yield) of the less polar triol