TOTAL SYNTHESIS OF (±)-α-CYCLOPIAZONIC ACID

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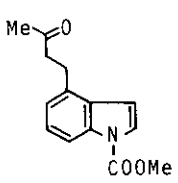
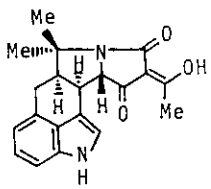
Abstract —— (±)-α-Cyclopiazonic acid (2) was synthesized from 1-methoxycarbonyl-4-(3-oxo-1-butyl)indole (1) by way of 17, 18, and 19, using a reaction of MeLi with a pyrroline derivative 33 in the presence of $BF_3 \cdot Et_2O$.

Some time ago, we reported a novel reaction for the preparation of 4-alkylindoles from 1-methoxycarbonylpyrrole.[1] 1-Methoxycarbonyl-4-(3-oxo-1-butyl)indole (1) obtained by this procedure has served as a good starting material in synthesizing a number of ergot alkaloids.[2] Here we describe a further utilization of 1 for a total synthesis in the racemic form of α-cyclopiazonic acid (2), a mycotoxin isolated first from Penicillium cyclopium Westling,[3,4] accompanied by the related alkaloids, cyclopiazonic acid imine (3) and β-cyclopiazonic acid (bissecodehydrocyclopiazonic acid) (4).[5] This study confirms the proposed structures of 2 and 3,[6] since the latter has been derived from 2 by treatment with aqueous ammonia.[5]



1



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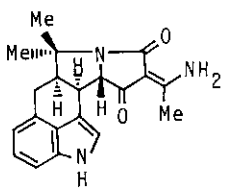

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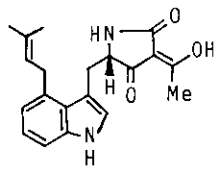

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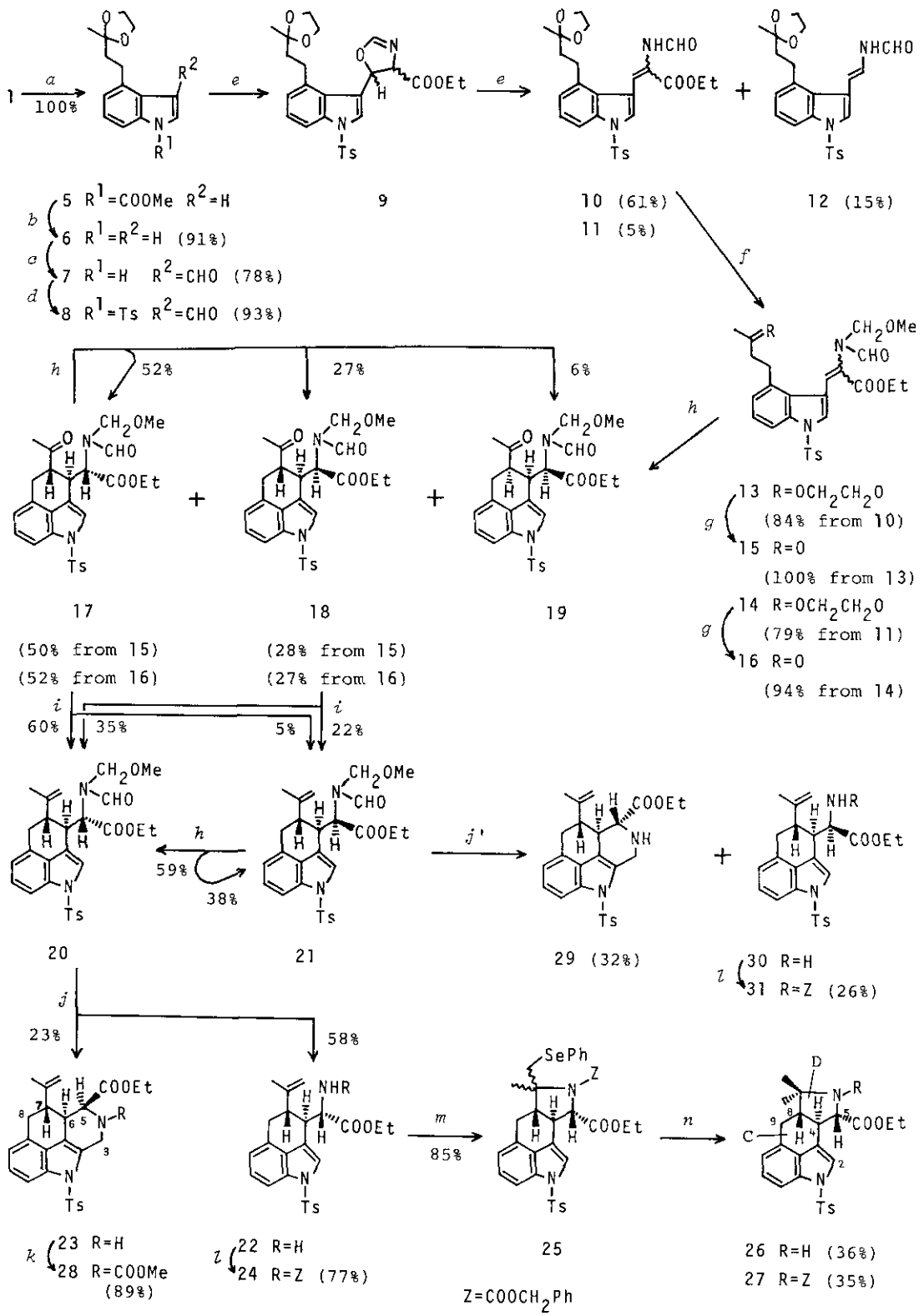
3-Formylindole derivative 7, readily prepared from 1 by way of 5 and 6 using conventional reaction steps depicted in Chart 1, was tosylated to afford 8 in order to make the formyl function sufficiently reactive to a carbanion generated from ethyl isocyanoacetate[7] and t-BuOK in THF. An oxazolidine derivative 9[8] was a reaction product at first but further addition of t-BuOK cleaved the oxazolidine ring to form the desired compounds 10 and 11 in 61% and 5% yields, respectively,


a
100%
e
e
NHCHO
COOEt
Ts
5 R1=COOMe R2=H
b
6 R1=R2=H (91%)
c
7 R1=H R2=CHO (78%)
d
8 R1=Ts R2=CHO (93%)
9
10 (61%)
11 (5%)
12 (15%)
f
h
52%
27%
6%
CH2OMe
CHO
17
18
19
(50% from 15)
(52% from 16)
(28% from 15)
(27% from 16)
13 R=OCH2CH2O
(84% from 10)
g
15 R=O
(100% from 13)
14 R=OCH2CH2O
(79% from 11)
16 R=O
(94% from 14)
i
60%
35%
5%
22%
20
21
59%
38%
j'
29 (32%)
30 R=H
l
31 R=Z (26%)
j
23%
58%
k
23 R=H
28 R=COOMe
(89%)
22 R=H
24 R=Z (77%)
m
85%
SePh
25
Z=COOCH2Ph
n
D
26 R=H (36%)
27 R=Z (35%)

a: $HOCH_2CH_2OH$, p-TsOH, C_6H_6, reflux, 1 h. *b*: 2% KOH in MeOH-DME-H_2O (3:1:1), r.t., 1.5 h. *c*: $POCl_3$-DMF in Et_2O-DMF, 0°C → r.t., 30 min. *d*: p-TsCl, Et_3N, CH_2Cl_2, r.t., 1h. *e*: $CNCH_2COOEt$, t-BuOK, THF, -81 – -20°C, 1 h; and then t-BuOK, -20°C, 30 min. *f*: 50% NaH, DMF, 0°C, 20 min; and then $ClCH_2OMe$ in THF, -83 → -20°C, 30 min. *g*: acetone, p-TsOH, r.t., 14 h. *h*: DBU, C_6H_6, reflux, 6 h from 15, 16 or 21, 3.5 h from 17. *i*: (i) $Ph_3P{=}CH_2$, THF, -80°C, 20 min; (ii) 50% NaH, DMF-THF (2:3), 0°C → r.t., 1 h. *j*: 1 N HCl in DMSO-EtOH-H_2O (1:1:1), reflux, 2 h. *j'*: 1 N HCl in DMSO-EtOH-H_2O (2:2:1), reflux, 5 h. *k*: ClCOOMe, Et_3N, CH_2Cl_2, -20°C → r.t., 1 h 15 min. *l*: $ClCOOCH_2Ph$, Et_3N, CH_2Cl_2, -20°C → r.t. *m*: PhSeCl, SiO_2, CH_2Cl_2, -82°C, 15 min and then r.t., 1.5 h. *n*: Raney Ni (W-2), EtOH, reflux, 4 h.

Chart 1

accompanied by the formation of 12 in 15% yield. The geometrical stereostructures of 10 and 11 remain undetermined. The formamide function in 10 and 11 was protected by the methoxymethyl group to give 13 and 14, and the ethylene ketal group was removed to afford 15 and 16, which were ready for the cyclization induced by the intramolecular Michael reaction. This was achieved by heating either 15 or 16 with DBU in refluxing benzene, and tricyclic compounds 17 and 18 were obtained in 50% and 28% or 52% and 27% yields, accompanied by the formation of the third product 19 with inseparable contaminants in a small amount. The respective yields of the three products reflected the ratio of the equilibrium during the Michael addition reaction and this was verified by the observation that the same treatment of 17 as above produced 18 and 19 in 27% and 6% yields with the recovery of 17 in 52% yield.

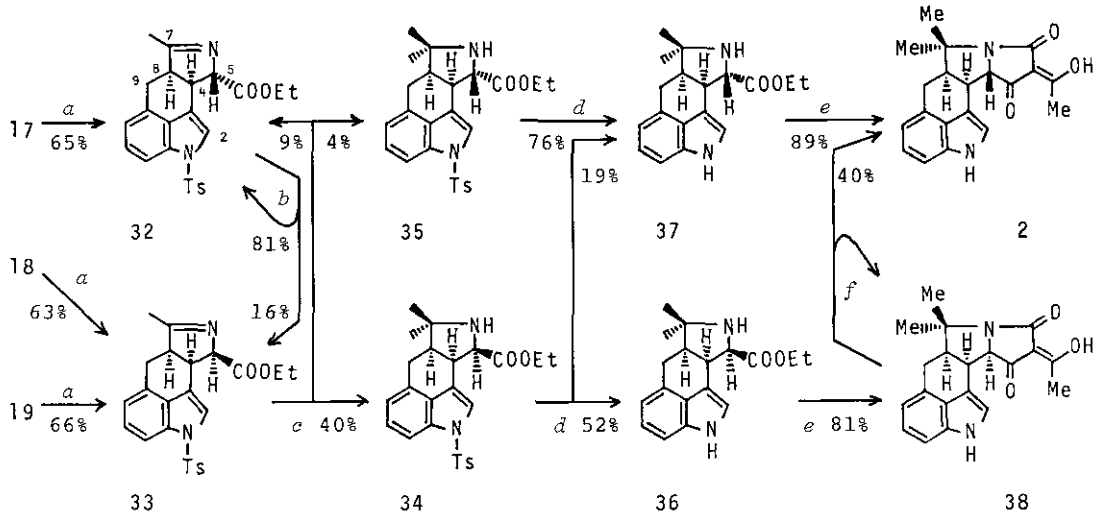
Stereochemistry of the tricyclic compounds 17 and 18 is determined as follows. The reaction of $Ph_3P{=}CH_2$ with 17 or 18, followed by treatment with NaH, furnished a mixture of 20 and 21 with a partial isomerization of the COOEt group in either case, 20 being thermodynamically more favored. This fact was supported by the predominant formation of 20, when 21 was refluxed with DBU. Acid hydrolysis of the N_b-protecting groups of 20 afforded the expected primary amine 22 in 58% yield, together with a by-product 23 in 23% yield. The amino group in 22 was protected again by the benzyloxycarbonyl group to give 24 and this was treated with PhSeCl in the presence of SiO_2[9] to produce tetracyclic compound 25 having the phenylselenyl function, which was removed reductively with Raney Ni in refluxing EtOH to yield 26 and 27. The ^1H NMR spectrum[10] of 26 exhibits a big coupling value (J=12.5 Hz) between H-4 and H-8, suggesting that 26 possesses an undesired trans stereochemistry of the C/D ring juncture.

The structure of the by-product obtained at the acid hydrolysis of 20 is considered

to be 23 according to the precedent reported by Goto et al.,[11] as a cyclization product of an $-N=CH_2$ moiety of an intermediate to the C-2 position of the N-tosylindole function, which seems to be still nucleophilic probably due to the styrene reactivity. By-product 23 was converted to a methoxycarbonyl derivative 28, whose ^1H NMR spectrum[12] revealed the stereochemistry at the C-5, C-6, and C-7 positions as shown by analysis of the coupling pattern of H-5 (d, J = 6 Hz) and H-6 (dddd, J = 12, 6, 3, 3 Hz), the latter being involved in the long-range coupling with each of the methylene protons at C-3 position. This fact together with the ^1H NMR spectrum of 26 confirms the stereostructures of 20 and its COOEt epimer 21, and therefore, strongly suggests those of 17 and 18. The similar acid treatment of 21 afforded another set of compounds 29 and 30, which were separated and characterized after converting 30 into 31. This indicates that the stereocenter of the amino acid ester part remained unaffected by the acid treatment.

The acid hydrolysis of the ketone derivatives 17, 18, and 19 provides key compounds for the total synthesis (Chart 2); i.e., a ketimine derivative 32 was a product from 17, whereas another ketimine 33 was the sole product from either 18 or 19. The structures of 32 and 33 are supported by the following facts, keeping in mind the above argument about the stable nature of the COOEt group with an acid. (i) The relationship between the C and D rings of 32 is demonstrated to be cis by its ^1H NMR spectrum,[13] in which a relatively small coupling value ($J_{4,8}$ = 7.5 Hz) compared to that of 26 was deduced from the proton signal at the C-4 position. (ii) Compound 33 is an epimer of 32 with respect to the configuration of the COOEt group, because 32 was isomerized in part to 33 by heating with DBU. The predominant recovery of 32 implies the thermodynamically stable character of its COOEt function. (iii) A high field shift of the methyl proton signal (0.78 ppm) of the COOEt group was observed in the ^1H NMR spectrum[14] of 33 and this can be explained only by the ring current effect of the indole ring, offering strong evidence for the structure 33, where the methyl group is closely located above the aromatic ring. Therefore, in summary, epimerization at the C-8 position has taken place during the acid treatment of 17 and 18 to yield C/D cis ketimines 32 and 33 corresponding to the stereochemistry of α-cyclopiazonic acid (2) and iso-α-cyclopiazonic acid (38).[3] At the same time, the structure of 19 is established as shown.

Introduction of the methyl group into the ketimine function requires a quite novel



a: 1 N HCl in EtOH-H_2O (4:1), reflux, 3 h from 17, 4 h from 18, 6 h from 19. *b*: DBU, C_6H_6, reflux, 3 h. *c*: (i) $BF_3 \cdot Et_2O$, THF, 0°C, 5 min; (ii) MeLi in Et_2O, ~80 – -65°C, 45 min. *d*: (i) 10% KOH in EtOH-H_2O (3:1), reflux, 3 h; (ii) *p*-TsOEt, EtOH, reflux, 14 h. *e*: (i) diketene, CH_2Cl_2, reflux, 1 h for 38, 2 h for 2; (ii) t-BuOK, THF-EtOH (5:1), 0°C → r.t., 19.5 h for 38, 15 h for 2. *f*: Et_3N, C_6H_6, reflux, 15 h.

Chart 2

method, since the addition to the ketimine system of an alkylmetallic reagent is generally unattainable, especially with the neighboring hydrogen atoms such as C_7-Me and C_8-H.[15] In order to overcome this difficulty, a special device consisting of an initial formation of a complex with $BF_3 \cdot Et_2O$, followed by the addition of MeLi was applied to 33,[16] utilizing the knowledge about a possible steric hindrance of the COOEt group, which was suggested by the above-mentioned NMR phenomenon. Requisite compounds 34 and 35 were obtained in 40% and 4% yields, respectively, accompanied by the formation of 32 in 9% yield. The tosyl group was removed at this stage by warming 34 and 35 with caustic alkali. Reesterifying the resulting amino acids with ethyl *p*-toluenesulfonate[17] afforded a mixture of 36 and 37 from 34 but only 37 from 35. Compound 36 was treated successively with diketene[18] in CH_2Cl_2 and t-BuOK in a mixture of THF and EtOH to produce (±)-iso-α-cyclopiazonic acid (38), which was identical with the authentic sample (UV, IR, MS, and ^1H NMR) prepared from natural α-cyclopiazonic acid according to the literature.[3] Treating 37 the same as above completed the synthesis of (±)-α-cyclopiazonic acid (2), identified with the natural specimen (TLC, UV, IR, MS, and ^1H

NMR), confirming its proposed structure. Treatment of (±)-38 with Et_3N in refluxing benzene afforded a 5:2 mixture of (±)-2 and (±)-38, whose recrystallization from MeOH yielded a further crop of (±)-2 in 40% yield.[19]

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10. ^1H NMR of 26 ($CDCl_3$, 90 MHz) δ: 1.17 (s, Me), 1.28 (s, Me), 1.41 (t, J = 7.5

Hz, $COOCH_2\underline{CH}_3$), 1.98 (ddd, J = 12.5, 10.5, 5 Hz, H-8), 2.24 (br s, NH) 2.32 (s, $SO_2C_6H_4\underline{CH}_3$), 2.68 (dd, J = 15.5, 10.5 Hz, H-9), 2.91 (dd, J = 15.5, 5 Hz, H'-9), 3.11 (ddd, J = 12.5, 10, 2 Hz, H-4), 3.88 (d, J = 10 Hz, H-5), 4.35 (br q, J = 7.5 Hz, $COOCH_2\underline{Me}$), 7.39 (d, J = 2 Hz, H-2).

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12. ^{1}H NMR of 28 ($CDCl_3$, 60°C, 90 MHz) δ: 1.07 (t, J = 7.5 Hz, $COOCH_2\underline{CH}_3$), 1.87 (br s, $=\underset{|}{C}-\underline{CH}_3$), ca. 2.21-2.59 (m, H-7), 2.31 (s, $SO_2C_6H_4\underline{CH}_3$), 2.77 (dd, J = 18.5, 6 Hz, H-8), 2.97 (dd, J = 18.5, 9.5 Hz, H'-8), 3.38 (dddd, J = 12, 6, 3, 3 Hz, H-6), 3.74 (s, COOMe), ca. 3.74-4.20 (m, $COOCH_2\underline{Me}$), 4.74 (dd, J = 18, 3 Hz, H-3), 4.96 and 5.00 (br s each, $=CH_2$), 5.33 (dd, J = 18, 3 Hz, H'-3), 5.43 (d, J = 6 Hz, H-5).
13. ^{1}H NMR of 32 ($CDCl_3$, 90 MHz) δ: 1.36 (t, J = 7.5 Hz, $COOCH_2\underline{CH}_3$), 2.13 (d, J = 1.5 Hz, C_7-Me), 2.31 (s, $SO_2C_6H_4\underline{CH}_3$), 2.66 (dd, J = 18, 11 Hz, H-9), 3.01-3.44 (m, H-8 and H'-9), 3.76 (dd, J = 7.5, 7.5 Hz, H-4), 4.33 (q, J = 7.5 Hz, $COO\underline{CH}_2Me$), 4.44 (br d, J = 7.5 Hz, H-5).
14. ^{1}H NMR of 33 ($CDCl_3$, 90 MHz) δ: 0.78 (t, J = 7.5 Hz, $COOCH_2\underline{CH}_3$), 2.12 (d, J = 1.5 Hz, C_7-Me), 2.31 (s, $SO_2C_6H_4\underline{CH}_3$), 2.89-3.38 (m, H-8, H-9, and H'-9), 3.79 (q, J = 7.5 Hz, $COOCH_2\underline{Me}$), 3.93 (br dd, J = 8, 7 Hz, H-4), 4.94 (br d, J = 8 Hz, H-5).
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