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FUMARIACEAE ALKALOIDS INCLUDING THE BIOGENETIC PRECURSOR OF CULARINE

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Key Word Index—*Corydalis claviculata*; Fumariaceae; benzylisoquinoline alkaloids; cularines; (+)-crassifoline; (+)-sarcocapnidine; (+)-claviculine; (+)-*O*-methylcularicine.

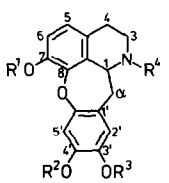
Abstract—*Corydalis claviculata* has yielded (+)-crassifoline, the first 7,8,3′,4′-oxygenated benzylisoquinoline and biogenetic precursor of cularine, as well as the new cularine alkaloids (+)-sarcocapnidine, (+)-claviculine and (+)-*O*-methylcularicine.

INTRODUCTION

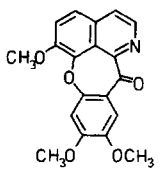
The cularines, whose occurrence except for one compound is limited to the Fumariaceae, form a small group of isoquinoline alkaloids [1]. They have been assumed to arise by direct oxidative coupling of a 7,8,3′,4′-oxygenated benzylisoquinoline [2]. This has been proved by feeding experiments [3].

Most cularines are substituted in positions 7, 3′ and 4′ as the known cularine (**1**), cularidine (**2**), cularicine (**3**) and cularimine (**4**), as well as the recently characterized culacorine (**5**), norcularicine (**6**) and oxocularine (**7**) [4, 5]. Sarcocapnine (**8**) and oxosarcocapnine (**9**), however, show an isomeric 7,4′,5′-substitution pattern [6] that had previously only been described for the morphine–cularine dimer cancentrine [7]. Another interesting completely different substituted compound, gouregine (**10**), occurs only in the Annonaceae and has a different biogenetic origin [8].

Corydalis claviculata, a tendril climbing, annual plant, is the only member of the genus *Corydalis* bearing cularine alkaloids. Manske reported the isolation of bases **1–3** together with stylopine and protopine [9]. Recently, compounds **5–7** have also been found [4, 5]. We now wish to describe the isolation of (+)-crassifoline (**11**), the biogenetic precursor of the cularine alkaloids, the two cancentrine-type bases (+)-sarcocapnidine (**12**) and (+)-claviculine (**13**) as well as (+)-*O*-methylcularicine (**14**) and (+)-cularimine (**4**) together with (+)-reticuline (**15**), (−)-cheilanthifoline (**16**), (−)-scoulerine (**17**) and (+)-thaliporphine (**18**) from *C. claviculata*. A preliminary report has already been published [10]. Compounds **11–13** have also been independently isolated by Boente *et al.* from *Sarcocapnos crassifolia* (Fumariaceae) [11].



	R^1	R^2	R^3	R^4
1	CH_3	CH_3	CH_3	CH_3
2	H	CH_3	CH_3	CH_3
3	H	$-CH_2-$		CH_3
4	CH_3	CH_3	CH_3	H
5	H	CH_3	H	CH_3
6	H	$-CH_2-$		H



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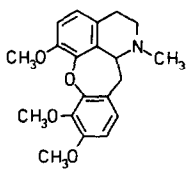

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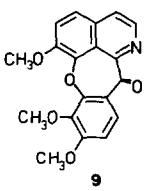

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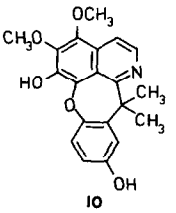

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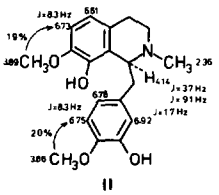

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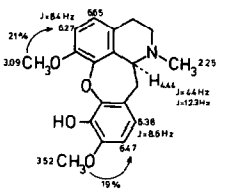

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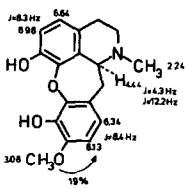

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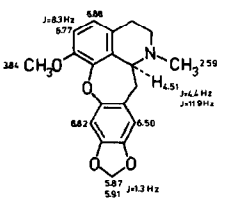

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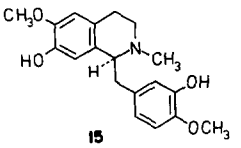
*To whom correspondence should be addressed.



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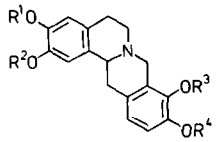
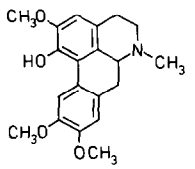


	R^1	R^2	R^3	R^4
16	CH_3	H	$-CH_2-$	
17	CH_3	H	H	CH_3



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RESULTS AND DISCUSSION

Extraction and work-up of the dried plant yielded (+)-crassifoline (**11**), the first 7,8,3',4'-oxygenated benzylisoquinoline from a natural source, as an oil, $[\alpha]_D^{22}$ +37.6°, which analysed for $C_{19}H_{23}NO_4$. Addition of sodium hydroxide caused a bathochromic shift of the UV spectrum, indicating the presence of phenolic hydroxyl groups; acetylation established two. The mass spectrum exhibited no significant $[M]^+$. The base peak at *m/z* 192 is due to the isoquinoline part of the molecule. The minor peak at *m/z* 137 represents the benzyl moiety. Chemical ionization generated a $[M+1]^+$ peak at *m/z* 330.

The ^1H NMR spectrum is summarized in formula **11**. The AB spin system δ 6.61 and 6.73 (J = 8.3 Hz) reveals the 7,8-substitution pattern of the isoquinoline. The downfield shift of the pair of doublets corresponding to the C-1 methine proton is caused by the oxygen function at C-8 [12]. The positions of the methoxyl groups were determined by NOE difference studies [13]. Enhancement of the signals corresponding to H-6 and H-5' assigns positions 7 and 4' to the methoxyl functions, placing the hydroxyl groups at 8 and 3'. The spectroscopic data are in agreement with the spectrum of the synthetic racemate **11** [14]. The CD spectrum of crassifoline (**11**) revealed two negative Cotton effects (CE) at λ 276 and 232 nm associated with the ^1L_b- and ^1L_a-band, respectively, indicating *P*-helicity of the 7,8-substituted tetrahydroisoquinoline system [15, 16]. Thus, **11** possesses the *S*-configuration.

(+)-Sarcocapnidine (**12**), $C_{19}H_{21}NO_4$, crystallized from methanol as colourless needles, mp 118°. The phenolic character of **12**, indicated by a bathochromic shift of the UV maxima upon addition of sodium hydroxide, was proved by acetylation. The mass spectrum showed a base peak at *m/z* 327 representing the $[M]^+$, and no characteristic fragmentation, except at *m/z* 174, revealing the 7-methoxy substitution [17]. This fragmentation pattern is different from that of 3',4'-oxygenated cularines which exhibit the $[M-15]^+$ ion as the base peak due to the loss of a methyl from the 3'-OMe group forming a stabilized *p*-quinonoid ion [18]. Because of the absence of a 3'-OMe group in **12** and the stability of the cularine skeleton, the parent ion forms the base peak. This finding opens up the possibility of deducing the substitution pattern of cularine alkaloids from their mass spectra.

The chemical shift assignments of the ^1H NMR spectrum in C_6D_6, as outlined in formula **12**, were confirmed by double resonance experiments. The downfield pair of doublets centred at δ 4.44 (J = 4.4/12.3 Hz) is characteristic of the cularine skeleton and is due to the C-1 methine proton [18]. The two AB quartets in the aromatic region indicate the cancentrine-like 7,4',5'-substitution pattern. Interestingly, the H-2' doublet showed an additional splitting caused by long-range coupling with the C-α protons. NOE difference studies confirmed the positions of the methoxyl groups.

The configuration of sarcocapnidine (**12**) was shown to be *S* by comparison of the CD spectra of **12** and *S*-(+)-cularine (**1**). Both curves exhibit two negative Cotton effects attributed to the ^1L_b- and ^1L_a-bands and increasing $\Delta\varepsilon$ values in the lower wavelength region. A small positive CE at λ 292 nm, as found in cularine (**1**), could not be observed in the spectrum of **12** and may be caused by the different substitution patterns as already known for aporphine and protoberberine alkaloids [19, 20].

(+)-Claviculine (**13**), $C_{18}H_{19}NO_4$, furnished colourless prisms, mp 126°. The two phenolic hydroxyl groups were rationalized by acetylation. Owing to the isomeric substitution, the base peak of the mass spectrum, at *m/z* 313, corresponds to the $[M]^+$. The fragment at *m/z* 161 indicates that a phenolic function is attached to ring A [17]. The same information was obtained from the ^1H NMR spectrum in $CDCl_3$ solution. Our studies, confirmed by literature data [5, 11], revealed that the AB quartet corresponding to H-5 and H-6 in the case of a 7-OMe substitution collapses to a two-proton singlet near δ 6.80 when ring A is bearing a hydroxyl group. The ^1H NMR spectrum in benzene, summarized in formula **13**, was confirmed by double resonance experiments. It revealed the isomeric 4',5'-substitution. The 4'-OMe group was proved by NOE difference measurements. Both the *dextro* rotation and the two negative CD maxima point to the *S*-configuration of **13**. Accordingly, claviculine (**13**) is the first diphenolic cancentrine-type cularine alkaloid.

(+)-*O*-Methylcularicine (**14**), $C_{19}H_{19}NO_4$, was obtained as an oil. According to the spectral data, **14** carries no hydroxyl function. However, the mass spectrum showed in addition to the intense $[M]^+$ at *m/z* 325 and *m/z* 174 for the methoxy substituted isoquinoline part the base peak at *m/z* 308 $[M-17]^+$. High-resolution mass spectrometry showed the lost fragment to have *m/z* 17.0046 which corresponds to a hydroxyl group (calc. 17.0027). Therefore we re-investigated the spectrum of cularicine (**3**) isolated by us as well as the spectra of an authentic sample of **3** from Manske's collection and its *O*-acetyl derivative. All samples exhibited a $[M-17]^+$ peak. These findings differ from the data found by Kametani *et al.* [17], who reported a significant $[M-15]^+$ ion in the mass spectrum of cularicine (**3**) which they attributed to the loss of a methyl. This could not be observed by us; on the other hand, they did not mention a $[M-17]^+$ peak. It seems, therefore, that the methylenedioxy moiety leads to a fragmentation pathway different from that of other cularine alkaloids The ^1H NMR spectrum of **14** revealed the presence of a methoxyl and a methylenedioxy group. The latter appears as an AB spin system. Conclusive proof

of the structure was provided by TLC and spectral comparison of natural **14** and a sample prepared by *O*-methylation of (+)-cularicine (**3**) with diazomethane, which further confirms the *S*-configuration of **14**.

The known alkaloids (+)-curarine (**1**), (+)-cularidine (**2**), (+)-cularicine (**3**) and (+)-cularimine (**4**) were identified by spectral data and in part (species **3** and **4**) by comparison with authentic samples. The identity of **4** was furthermore proved by Eschweiler–Clarke methylation to generate (+)-curarine (**1**). Cularimine (**4**), previously only described for *Dicentra eximia* [21], was isolated from *C. claviculata* for the first time by us.

Of interest is the finding that compounds **5**, **6** and **7**, which have been isolated from *C. claviculata* by a French group [5], could not be found in the species we collected in the vicinity of Bremen (F.R.G.). On the other hand, the alkaloids **4**, **11**, **12** and **13** were not described for the French plant. Thus, chemical races may be the cause of such differences.

In addition, (+)-reticuline (**15**), (−)-cheilanthifoline (**16**), (−)-scoulerine (**17**) and (+)-thaliporphine (**18**) as well as (−)-stylopine and protopine were isolated. The bases were identified by their spectral data [22–26] and by comparison with authentic samples. (+)-Thaliporphine (**18**), known from *Thalictrum* species (Ranunculaceae) [26], is the first aporphine alkaloid from *C. claviculata*.

EXPERIMENTAL

Mps are uncorr. ^{1}H NMR spectra including double resonance and NOE difference studies were recorded at 300 MHz (FT) in $CDCl_3$ or C_6D_6 solns with TMS as internal standard. The samples were degassed prior to measurements. ^{13}C NMR (broad band decoupled) were recorded at 22.6 MHz (FT) in $CDCl_3$. Chemical shifts marked with an asterisk are interchangeable. EIMS were determined at 70 eV, CIMS with isobutane at 120°. CD spectra were measured in EtOH. Acetylation was carried out at room temp. with Ac_2O–pyridine (1:1) for 24 hr.

Extraction and isolation. Dried plant material (*ca* 850 g) was exhaustively extracted with EtOH. After evapn of solvent, the residue was dissolved in 500 ml 1 M H_2SO_4 and washed × 3 with 500 ml Et_2O. The aq. soln was made alkaline to pH *ca* 8 and extracted × 3 with 500 ml Et_2O. The Et_2O layer was concd under red. pres. and extracted × 3 with 50 ml 1 M NaOH. The organic solvent was removed to yield 4.43 g of alkaloids (fraction I). CC on silica gel with a CH_2Cl_2–MeOH gradient afforded (+)-curarine (**1**) (2.31 g), (+)-curarimine (**4**) (35 mg), (+)-*O*-methylcularicine (**14**) (30 mg), (−)-stylopine (200 mg) and protopine (1.72 g). The above alkaline soln was brought to pH *ca* 8 and extracted × 3 with 200 ml Et_2O. Evapn of solvent yielded 4.45 g of alkaloids (fraction II). This fraction was subjected to CC in the same manner to afford (+)-cularidine (**2**) (2.29 g), (+)-cularicine (**3**) (915 mg), (+)-crassifoline (**11**) (40 mg), (+)-sarcocapnidine (**12**) (160 mg), (+)-claviculine (**13**) (170 mg), (+)-reticuline (**15**) (15 mg), (−)-cheilanthifoline (**16**) (90 mg), (−)-scoulerine (**17**) (75 mg) and (+)-thaliporphine (**18**) (80 mg).

(+)-*Crassifoline* (**11**). Colourless oil; $[\alpha]_D^{22}$ +37.6° (EtOH; *c* 0.1); UV λ_{max}^{EtOH} nm (log ε): 207 (4.69), 226 sh (4.17), 280 (3.71); ^{13}C NMR ($CDCl_3$): δ 23 17 (C-4), 38.68 (C-α), 42.35 (NMe), 45.10 (C-3), 55.83 (OMe), 56.01 (OMe), 60.23 (C-1), 109.13* (C-6), 110.57* (C-5'), 115.84 (C-2'), 119.16 (C-5), 120.56 (C-6'), 124.26 (C-8a), 127.10 (C-4a), 134.11 (C-1'), 142.52 (C-3'), 144.34* (C-8), 145.04* (C-4'), 145.36* (C-7); EIMS 70 eV *m/z* (rel. int.): 329 $[M]^+$ (0.1), 192 $[C_{11}H_{14}NO_2]^+$ (found: 192.1014; requires: 192.1024) (100); 177 $[192-Me]^+$ (18), 137 $[C_8H_9O_2]^+$ (found: 137.0601; requires: 137 0602) (8); CIMS *m/z* (rel. int.): 330 $[M+H]^+$ (100); CD Δε (nm): −2.13 (276), −4.54 (232). (Found: C, 69.01; H, 7.01; N, 4.12. $C_{19}H_{23}NO_4$ requires: C, 69.27; H, 7.04; N, 4.25%.)

(+)-*Sarcocapnidine* (**12**). Colourless needles, mp 118°; $[\alpha]_D^{22}$ +368° (EtOH; *c* 0.1); UV λ_{max}^{EtOH} nm (log ε): 207 (4.72), 220 sh (4.31), 272 (3.53), 276 (3.55); ^{1}H NMR ($CDCl_3$): δ 2.59 (3H, *s*, NMe), 2.76–3.48 (6H, *m*, aliphatic CH_2), 3.87 (3H, *s*, OMe), 3.88 (3H, *s*, OMe), 4.49 (1H, *dd*, *J* = 4.4 and 12.3 Hz, H-1), 6.51 (1H, *d*, *J* = 8.6 Hz, H-2'), 6.62 (1H, *d*, *J* = 8.6 Hz, H-3'), 6.75 (1H, *d*, *J* = 8.4 Hz, H-6), 6.91 (1H, *d*, *J* = 8.4 Hz, H-5), 7.14 (1H, *br s*, OH); ^{13}C NMR ($CDCl_3$): δ 25.58 (C-4), 34.05 (C-α), 42.29 (NMe), 47.48 (C-3), 55.75 (OMe), 56.01 (OMe), 56.42 (C-1), 108.13* (C-3'), 109.63* (C-6), 120.24* (C-2'), 120.91* (C-1'), 124.93 (C-5), 127.25 (C-4a), 132.14 (C-8a), 137.65 (C-5'), 143.08* (C-6'), 144.48* (C-8), 145.86* (C-4'), 148.06* (C-7); EIMS 70 eV *m/z* (rel. int.) 327 $[M]^+$ (100), 312 $[M-Me]^+$ (36), 310 $[M-OH]^+$ (27), 296 $[M-OMe]^+$ (16), 284 $[M-CH_2{=}N{-}Me]^+$ (26), 281 $[312-OMe]^+$ (53), 174 $[C_{11}H_{12}NO]^+$ (found 174.0914; requires: 174.0919) (44), 159 $[174-Me]^+$ (15), 148 $[C_9H_{10}NO]^+$ (17); CD Δε (nm): −1.46 (272), −13.78 (232), positive tail (228). (Found: 327 1470; $C_{19}H_{21}NO_4$ requires: 327.1470.)

(+)-*Claviculine* (**13**). Colourless prisms, mp 126°; $[\alpha]_D^{22}$ +404° (EtOH; *c* 0.1); UV λ_{max}^{EtOH} nm (log ε): 208 (4.52), 228 sh (4.05), 288 (3 49); ^{1}H NMR ($CDCl_3$): δ 2.59 (3H, *s*, NMe), 2.74–3.44 (6H, *m*, aliphatic CH_2), 3.58 (3H, *s*, OMe), 4.48 (1H, *dd*, *J* = 4.2 and 12.1 Hz, H-1), 6.58 (2H, 2, H-2', H-3'), 6.79 (2H, *s*, H-5, H-6); ^{13}C NMR ($CDCl_3$): δ 25.49 (C-4), 35.05 (C-α), 42.17 (NMe), 48 21 (C-3), 56.39 (OMe), 56.89 (C-1), 107.08 (C-3'), 113.82 (C-6), 121.21 (C-2'), 122.53 (C-1'), 125.28* (C-5), 125.87* (C-4a), 131.12 (C-8a), 137.29 (C-5'), 143.42* (C-8), 143 74* (C-6'), 145.81* (C-7), 146.18* (C-4'); EIMS 70 eV *m/z* (rel int.): 313 $[M]^+$ (100), 298 $[M-Me]^+$ (58), 296 $[M-OH]^+$ (46), 281 $[298-OH]^+$ (10), 271 $[M-CH_2{=}N{-}Me]^+$ (21), 161 $[C_{10}H_{11}NO]^+$ (found: 161.0853; requires: 161.0841) (12), 148 $[C_9H_{10}NO]^+$ (13); CD Δε (nm): −1.75 (273), −4.19 (232), positive tail (226). (Found: 313 1312; $C_{18}H_{19}NO_4$ requires: 313.1314.)

(+)-O-*Methylcularicine* (**14**). Colourless oil, $[\alpha]_D^{22}$ +283° (EtOH; *c* 0.3); UV λ_{max}^{EtOH} nm (log ε): 206 (4.47), 223 sh (4.10), 284 (3.72), 290 (3.73); EIMS 70 eV *m/z* (rel. int.). 325 $[M]^+$ (90), 310 $[M-Me]^+$ (25), 308 $[M-OH]^+$ (found: 308.1274; $C_{19}H_{18}NO_3$ requires: 308.1287) (100), 294 $[M-OMe]^+$ (34), 174 $[C_{11}H_{18}NO]^+$ (found: 174.0922; requires: 174.0919), (64), 159 $[174-Me]^+$ (19); (found: 325.1320; $C_{19}H_{19}NO_4$ requires: 325.1314).

Preparation of **14** (+)-Cularicine (**3**), 20 mg (6.4×10^{-2} mmol), was left overnight with *ca* 2 mmol CH_2N_2 in dry Et_2O. The solvent was removed under red. pres. to yield 18 mg **14** as an oil. R_f values, mass and ^{1}H NMR spectra were identical with those of natural **14**.

(+)-*Curarine* (**1**). CD Δε (nm): +1.28 (291), −3.42 (273), −12.82 (243), positive tail (227); the spectral data were in agreement with published values [9, 12, 17].

(+)-*Cularidine* (**2**). All spectra were identical with lit. data [9, 17].

(+)-*Cularicine* (**3**). EIMS 70 eV *m/z* (rel. int.): 311 $[M]^+$ (found: 311.1164; $C_{18}H_{17}NO_4$ requires: 311.1157) (88), 294 $[M-OH]^+$ (found: 294.1122; $C_{18}H_{16}NO_3$ requires: 294.1130) (100), 282 $[M-CHO]^+$ (13), 161 $[C_{10}H_{11}NO]^+$ (48); all other data were identical with lit. data [9, 17]; comparison to authentic sample (MS, ^{1}H NMR, R_f).

(+)-*Curarimine* (**4**). R_f values, mass and ^{1}H NMR spectra were identical with those of an authentic sample.

N-*Methylation of* **4**. **4** (10 mg) was dissolved in 2 ml of a mixture of HCO_2H–HCHO (1:1) and heated for 8 hr at 100°. Work-up afforded 4.5 mg **1**, identical with an authentic sample (MS, R_f).

(+)-*Reticuline* (**15**). Colourless oil; $[\alpha]_D^{22}$ +112° (MeOH; *c* 0.24); spectral data identical with lit. [22]; comparison with authentic sample (mmp, ^{1}H NMR, R_f).

(−)-*Cheilanthifoline* (**16**). Spectral data identical with lit. [23]; comparison with authentic sample (mmp, MS, ^{1}H NMR, R_f).

(−)-*Scoulerine* (**17**). Spectral data identical with lit. [24]; comparison with authentic sample (mmp, MS, ^{1}H NMR, R_f).

(−)-*Stylopine*. Spectral data identical with lit. [9, 24].

Protopine. ^{1}H NMR as lit. [25].

(+)-*Thaliporphine* (**18**). Colourless needles; $[\alpha]_D^{22}$ +42°; spectral data identical with lit. [26]; comparison with authentic sample (^{1}H NMR).

Acknowledgements—We are grateful to Dr. V. Wray for NOE measurements of **12**, to Prof. G. Snatzke for discussion of the CD spectrum of **11** and to Dr. D. Schmidt, Bayer AG, Wuppertal-Aprath, F.R.G., for lyophilization of the plant material. In addition, we wish to thank Professor D. B. MacLean for authentic samples of **3** and **4** from Professor Manske's collection, Professor E. Brochmann-Hanssen for a gift of natural **15** and **17**, Professor J. Slavik for **16** and Professor M. Shamma for a copy of the ^{1}H NMR spectrum of **18**.

REFERENCES

1. Shamma, M. (1972) *The Isoquinoline Alkaloids*. Academic Press, New York.
2. Abu Zarga, M. H., Miana, G. A. and Shamma, M. (1981) *Tetrahedron Letters* **22**, 541.
3. Blaschke, G. and Scriba, G. (1983) *Tetrahedron Letters* **24**, 5855.
4. Boente, J. M., Castedo, L., Rodriguez de Lera, A., Saa, J. M., Suau, R. and Vidal, M. C. (1983) *Tetrahedron Letters* **24**, 2295.
5. Allais, D. P. and Guinaudeau, H. (1983) *J. Nat. Prod.* **46**, 881.
6. Campello, M. J., Castedo, L., Saa, J. M., Suau, R. and Vidal, M. C. (1982) *Tetrahedron Letters* **23**, 239.
7. Clark, G. R., Manske, R H. F, Palenik, G. J., Rodrigo, R., MacLean, D. B., Baczynskyj, L., Gracey, D. E. F. and Saunders, J. K. (1970) *J. Am Chem. Soc* **92**, 4998.
8. Leboeuf, M., Cortes, D., Hocquemiller, R., Cave, A., Chiaroni, A. and Riche, C. (1982) *Tetrahedron* **38**, 2889.
9. Manske, R. H. F. (1940) *Can. J. Res.* **18B**, 97.
10. Blaschke, G. and Scriba, G. (1983) *Z. Naturforsch. Teil C* **38**, 670.
11. Boente, J. M., Castedo, L., Cuadros, R., Rodriguez de Lera, A., Saa, J. M., Suau, R. and Vidal, M. C. (1983) *Tetrahedron Letters* **24**, 2303.
12. Bhacca, N. S., Cymerman Craig, J., Manske, R. H. F., Roy, S. K., Shamma, M. and Slusarchyk, W. A. (1966) *Tetrahedron* **22**, 1467.
13. Hall, L. D. and Sanders, J. K. M. (1980) *J. Am. Chem. Soc.* **102**, 5703.
14. Kametani, T., Fukumoto, F. and Fujihara, M. (1971) *Bioorg. Chem.* **1**, 40.
15. Cymerman Craig, J., Lee, S. Y. C., Chan, R. P. K. and Wang, I. Y. F. (1977) *J. Am. Chem. Soc.* **99**, 7996.
16. Snatzke, G., Kajtar, M. and Werner-Zamojska, F. (1972) *Tetrahedron* **28**, 281.
17. Kametani, T., Shibuya, S., Kibayashi, C. and Sasaki, S. (1966) *Tetrahedron Letters* 3215.
18. Ohashi, M., Wilson, J. M., Budzkiewicz, H., Shamma, M., Slusarchyk, W. A. and Djerassi, C. (1963) *J. Am. Chem. Soc.* **85**, 2801.
19. Ringdahl, B., Chan, R. P. K., Cymerman Craig, J., Cava, M. P. and Shamma, M. (1981) *J Nat. Prod.* **44**, 80.
20. Ringdahl, B., Chan, R. P. K., Cymerman Craig, J. and Manske, R. H. F (1981) *J. Nat. Prod.* **44**, 75.
21. Manske, R. H. F (1938) *Can. J. Res.* **16B**, 81.
22. Brochmann-Hanssen, E. and Furuya, T. (1964) *Planta Med.* **12**, 328.
23. Haisova, K. and Slavik, J. (1973) *Collect. Czech. Chem. Commun.* **38**, 2307.
24. Chen, C. Y. and MacLean, D. B. (1968) *Can. J. Chem.* **46**, 2501.
25. Johns, S R., Lamberton, J. A., Tweeddale, H. J. and Willing, J. R. (1969) *Aust. J. Chem.* **22**, 2233.
26. Shamma, M., Shine, R. J and Dudock, B. S. (1967) *Tetrahedron* **23**, 2887