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Synthetic Applications of 2-Aryl-4-piperidones. VIII.[1] Synthesis of Methyl Indolo[2,3-*a*]quinolizidin-2-acetate

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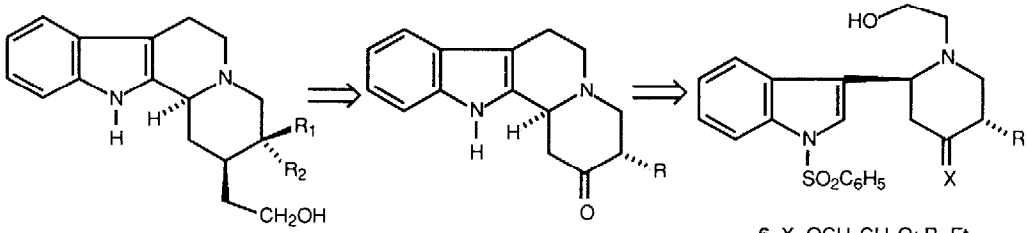
Abstract-*The synthesis of methyl indolo[2,3-a]quinolizidin-2-acetate (**21**) from 1-hydroxyethyl-2-[1-(phenylsulfonyl)-3-indolyl]piperidine-4-acetate (**16**) by an intramolecular cyclization induced by K^{t}BuO is described.*

In a previous paper[1] we reported the versatility of the intramolecular cyclization of *N*-hydroxyethyl-2-[1-(phenylsulfonyl)-3-indolyl]piperidines **6** and **7** by means of K^{t}BuO, which *via* an intermediate spiroindolenine transposed by the action of a Lewis acid, led to the synthesis of indolo[2,3-*a*]quinolizidin-2-ones such as **4** and **5** (Scheme 1).[2-5] On the other hand, *Corynanthe* alkaloids such as dihydrocorynantheol (**1**)[6] and its 20-epimeric derivative **2**[7] can be considered derived from indolo[2,3-*a*]quinolizidin-2-one **4**.[8]

In the present paper we describe the synthesis of methyl indolo[2,3-*a*]quinolizidin-2-acetate (**21**), a precursor of the basic framework **3** by a K^{t}BuO induced cyclization of the already functionalized 2-indolylpiperidine **16** (Scheme 2).

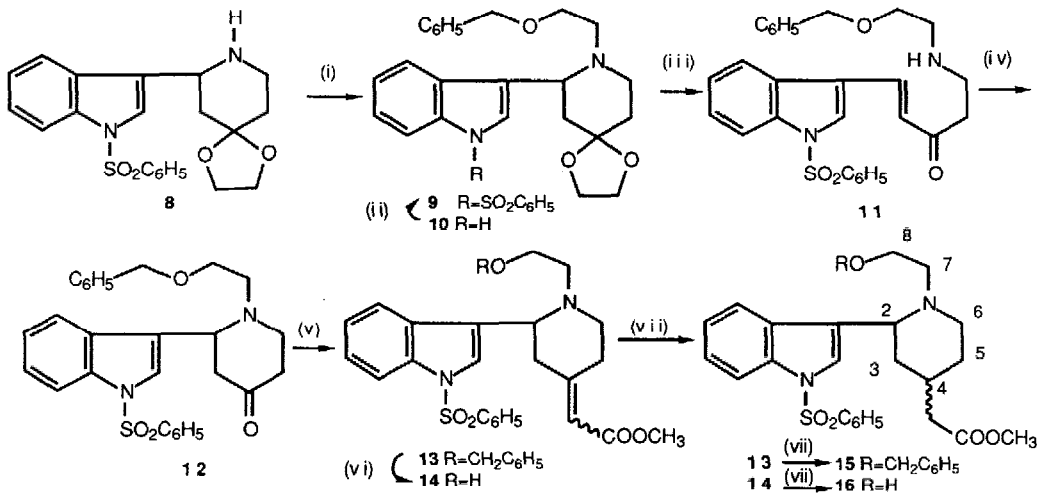


1 Dihydrocorynantheol (R_1=H; R_2=Et)
2 Corynantheidol (R_1=Et; R_2=H)
3 R_1=R_2=H

4 R=Et
5 R=H

6 X=OCH_2CH_2O; R=Et
7 X=OCH_2CH_2O; R=H

Scheme 1



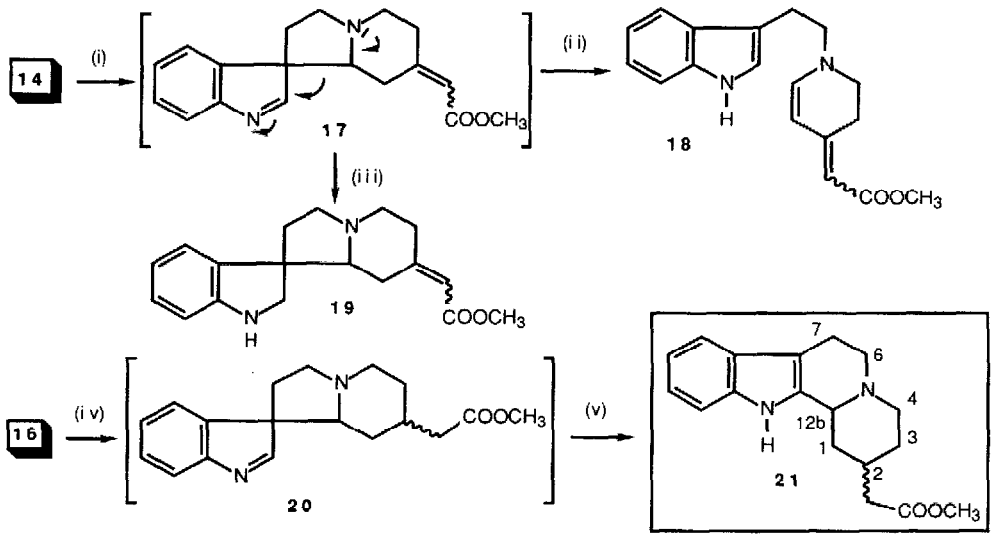
Reagents and Conditions: (i) $ICH_2CH_2OCH_2C_6H_5$ (1.5 eq), anh. K_2CO_3 , dry acetone (82% yield). (i i) 1. NaH, THF, Δ, 1 h. 2. $C_6H_5SO_2Cl$, THF, Δ, 1 h (83% yield). (i i i) 1:1 CH_3OH: 4*N* HCl, Δ, 7 h (77% yield). (i v) 1. CH_3OH, overnight, r.t. (67% yield). (v) $(EtO)_2POCH_2COOCH_3$ (1.2 eq) , NaH (1 eq), DME, (88% yield). (v i) $AlCl_3$, $C_6H_5N(CH_3)_2$, CH_2Cl_2 (80% yield). (v i i) H_2, Pd/C, EtOH (85 % yield).

Scheme 2

Alkylation of 2-indolylpiperidine **8**[1] with benzyloxyethyl iodide in the presence of K_2CO_3 furnished a mixture of compounds **9** and **10**.[9] The deprotection of the indole nitrogen atom in the basic reaction conditions was due to the long reaction times necessary to achieve complete alkylation. Nevertheless, treatment of **10** with sodium hydride and phenylsulfonyl chloride regenerated the desired compound **9**[10] in good yields. When the following hydrolysis of the acetal function of **9** was carried out under the usual conditions (4*N* HCl, CH_3OH, reflux, 3 h) only compound **11**[9] was obtained, resulting from a retro-Michael reaction, but which could easily be cyclized to the expected piperidone **12**[11] by simple stirring at room temperature in methanol. A Wadsworth-Emmons condensation of **12** with diethyl methoxycarbonylmethylphosphonate and sodium hydride furnished olefine **13** as a 2:1 *E/Z* mixture. Preparation of hydroxyethylpiperidine **14**[12] was achieved by selective debenzylation of **14** using aluminium trichloride and *N,N*-dimethylaniline in excellent yields.[13] The saturated analog **16**[14] was obtained by hydrogenation of **14** using Pd/C as the catalyst.

When the K^{t}BuO treatment[2] of **14** was followed by addition of $BF_3.Et_2O$, enaminoester **18**[15] was obtained in 25% yield after flash chromatography (Al_2O_3, CH_2Cl_2), thus showing that in this case, the five-membered ring opening by the nitrogen anchimeric assistance is favored with respect to the transposition of the indolenine.[4] In the absence of the acid treatment, a small proportion of **19** (10% yield) was also isolated, presumably as the result of

a disproportionation process. Finally, treatment of piperidine **16** with K^{t}BuO followed by a Lewis acid furnished methyl indolo[2,3-*a*]quinolizidin-2-acetate (**21**)[16] in 52% yield as a 1:1 epimeric mixture on C-2. With the synthesis of **21** we open a new approach to *Corynanthe* alkaloids which will be developed in the future.



Reagents and Conditions. (i) K^{t}BuO (2 eq), THF, 0°C, 30 min. (i i) $BF_3.Et_2O$ (1.5 eq) , THF, r.t. 1 h. (i i i) work-up; H_2O-CH_2Cl_2. (i v) K^{t}BuO (3 eq), THF, 0°C, 30 min. (v) BF_3-Et_2O (1.5 eq), r.t., 20 min.

Scheme 3

ACKNOWLEDGEMENTS

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9. All new compounds were identified by their spectral data and elemental analysis.
10. **9**: ^{1}H NMR (200 MHz) 1.75 (m, 2H, 3-He and 5-He), 1.98 (td, *J*=11, 5 Hz, 1H, 5-Ha), 2.10 (t, *J*=11 Hz, 1H, 3-Ha), 2.22 (dt, *J*= 13, 6 Hz, 1H, 7-H_A), 2.50 (t, *J*=11 Hz, 1H, 6-Ha), 2.73 (dt,*J*=13, 6 Hz, 1H, 7-H_B), 3.20 (br d, *J*=11 Hz, 1H, 6-He), 3.42 (t, *J*=6 Hz, 2 H, OCH_2), 3.72 (d, *J*=11 Hz, 1H, 2-Ha), 3.95 (s, 4H, OCH_2), 4.33 (s, 2H, OCH_2Ph), 7.05-7.50 (m, 11H), 7.80 (m, 3H), 7.95 (d, *J*=7 Hz, 1H, In-4H); ^{13}C NMR 34.7 (C-5), 42.2 (C-3), 51.0 (C-6), 53.0 (C-7), 58.0 (C-2), 64.4 (OCH_2), 68.4 (C-8), 72.8 ($PhCH_2O$), 107.2 (C-4), 113.9, 121.3, 123.3, 124.0, 125.1, 126.9, 127.7, 128.5, 129.4, 133.9, 135.6, 138.0.
11. **12**: IR ($CHCl_3$) 1713 (C=O); ^{1}H NMR 2.25-2.70 (m, 7H), 3.40 (t, *J*=6 Hz, 2 H, NCH_2CH_2), 3.95 (dd, *J*=10, 4 Hz, 1H, 2-Ha), 4.30 (s, 2H, OCH_2Ph), 7.00-7.40 (m, 12H), 7.73 (d, *J*=7 Hz, 1H, In-7H), 7.92 (d, *J*=7 Hz, 1H, In-4H). ^{13}C NMR 40.5 (C-5), 46.4 (C-3), 51.0 (C-6), 51.9 (C-7), 59.7 (C-2), 68.7 (C-8), 72.9 ($PhCH_2O$), 113.8, 121.2, 123.4, 124.2, 125.3, 126.7, 127.6, 128.4, 129.3, 133.9, 135.6, 138.3, 208.3 (C-4).
12. **14-(*E*)**: (major isomer) IR ($CHCl_3$) 3500 (OH), 1715 (C=O), 1650 (C=C); ^{1}H NMR 2.10-2.85 (m, 6H), 3.33 (m, 2H), 3.55-3.65 (m, 3H), 3.72 (s, 3H, OCH_3), 5.67 (s, 1H, =CH), 7.15-7.55 (m, 7H), 7.70 (d, *J*=7 Hz, 1H), 7.85 (d, *J*=7 Hz, 1H), 8.00 (d, *J*=7 Hz, 1H); ^{13}C NMR 28.8 (C-5), 43.0 (C-3), 50.8 (C-6), 51.7 (OCH_3), 54.6 (C-7), 58.4 (C-8), 60.7 (C-2), 113.9, 114.3, 120.3, 123.5, 123.8, 124.3, 125.2, 126.8, 128.9, 129.3, 133.9, 135.5, 138.0, 158.1, 167.0.
13. Akiyama, T.; Hirofuji, H. and Ozaki, S. *Tetrahedron Lett.*, **1991**, *32*, 1321.
14. **16** (*cis*): IR ($CHCl_3$) 3458 (OH), 1729 (COO); ^{1}H NMR 1.3-2.4 (m, 11H), 2.65 (m, 1H, 7-H_A), 3.20 (m, 1H, 7-H_B), 3.50 (m, 2H, CH_2OH), 7.10-7.40 (m, 5H), 7.50 (s, 1H, In-2H), 7.73 (d, *J*=7 Hz, 1H, In-4H), 7.85 (d, *J*=7 Hz, 2H), 7.95 (d, *J*=7Hz, 1H, In-7H); ^{13}C NMR 31.7 (C-5), 33.1 (C-4), 39.9 (C-3), 40.5 (*C*H_2COO) 51.3 (OCH_3), 52.3 (C-6), 55.2 (NCH_2), 58.2 (CH_2OH), 60.1 (C-2), 113.9 (In-C7), 120.5 (In-C2), 120.1 (In-C3), 123.3 (In-C4), 123.8 (In-C5), 125.0 (In-C6), 126.8 (C-*ortho*), 129.3 (C-*meta*), 133.9 (C-*para*), 135.6 (In-C7a), 137.9 (C-*ipso*), 173.0 (C=O).
15. **18**:IR ($CHCl_3$) 3470 (NH), 1700 (CO), 1595 (C=C); ^{1}H NMR 2.50 (t, *J*=7 Hz, 2H, C-5), 3.00 (t, *J*=7 Hz, In-CH_2), 3.15-3.25 (m, 2H, C-6), 3.45-3.50 (m, 2H, InCH_2CH_2), 3.63 and 3.68 (2 s, 3H each, OCH_3 **18**-(*E*) and **18**-(*Z*)), 4.95 (d, *J*=6 Hz, 1H, =CH), 6.25 (dd, *J*=6, 2 Hz, 1H, =CH), 6.38 (d, *J*=6 Hz, 1H, =CH), 7.00 (d, *J*=2 Hz, 1H, In-2H), 7.00-7.30 (m, 2H, In-H), 7.45 (d, *J*=7 Hz, 1H, In-7H), 7.58 (d, *J*=7 Hz, 1H, In-4H), 8.00 (br, 1H, NH).
16. **21**: ^{1}H NMR 2.48 (td, *J*=12, 4 Hz, 1H, 4-Ha), 2.75 (br d, *J*=12 Hz, 1H, 4-He), 2.90-3.15 (m, 2H, 6-H), 3.30 (br d, *J*=12 Hz, 1H, 12b-H), 3.70 (S, 3H, OCH_3), 7.00-7.30 (m, 3H, 8-H, 9-H, 10-H), 7.42 (d, *J*=7 Hz, 1H, 11-H), 7.85 (br, 1H, NH); ^{13}C NMR 21.5 (In-CH_2), 29.5 (C-3), 31.8 (C-2), 35.8 (C-1), 40.7 (*C*H_2COO), 51.5 (OCH_3), 53.1 (C-4), 55.1 (C-4), 59.4 (C-12b), 110.9 (C-11), 118.3, 119.5, 121.5 (C-8, C-9, C-10), 126.4 (C-7b), 135.5 (C-11a), 173.0 (COO).

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