CLAISEN ORTHOESTER REARRANGEMENT IN THE DIRECT PREPARATION OF DEPLANCHEINE DERIVATIVES POSSESSING A MALONYL GROUP AT C-15

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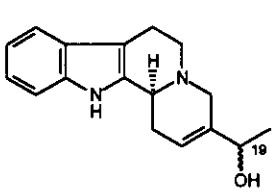
Abstract - The Claisen orthoester rearrangement utilizing allylic alcohols (**1**) and (**2**), and triethyl ortho-2-ethoxycarbonylacetate (= ethyl triethyl orthomalonate) (**4**) leads directly to deplancheine derivatives (**12 - 14**) possessing a malonyl group at C-15. Compounds (**12 - 14**) represent the prototype of highly desired intermediates for the preparation of *Corynanthé* alkaloids and similar compounds.

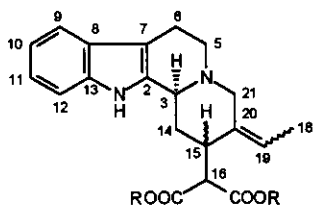
The Claisen orthoester rearrangement[1-5] provides a versatile synthetic method for the preparation of carbon-carbon bonds. Recently we described the stereoselective preparation of *Z*-isositsirikine derivatives by this method, utilizing allylic alcohols (**1**) and (**2**), and appropriate orthoesters.[6-8]

RESULTS AND DISCUSSION

The present paper reports our results concerning the applicability of the Claisen orthoester rearrangement utilizing allylic alcohols (**1**) and (**2**) in the direct preparation of deplancheine derivatives possessing a malonyl group at C-15.[9] Compounds of type (**3**) would represent highly desired intermediates for an easy preparation of *Corynanthé* alkaloids and similar structures.[10]



1 C-19 *R**
2 C-19 *S**



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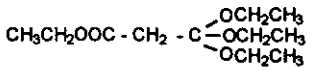
As orthoesters to be examined we chose triethyl ortho-2-ethoxycarbonylacetate (= ethyl triethyl orthomalonate) (**4**) and trimethyl ortho-2-methoxycarbonylacetate (= methyl trimethyl orthomalonate) (**5**).



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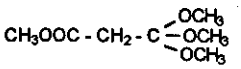
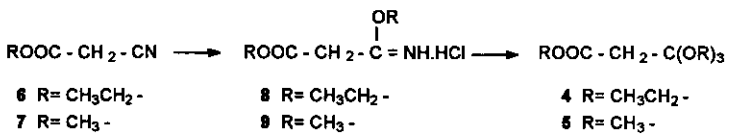


5

Compound (**4**) was prepared *via* the corresponding iminoester hydrochloride (= imidate hydrochloride) (**8**) by the "Pinner method"[11,12] from the commercially available ethyl 2-cyanoacetate (**6**).[13] The same method, applied to methyl 2-cyanoacetate (**7**),[14] in order to get compound (**5**), *via* the corresponding iminoester hydrochloride (**9**), was less successful and it was abandoned (Scheme 1).



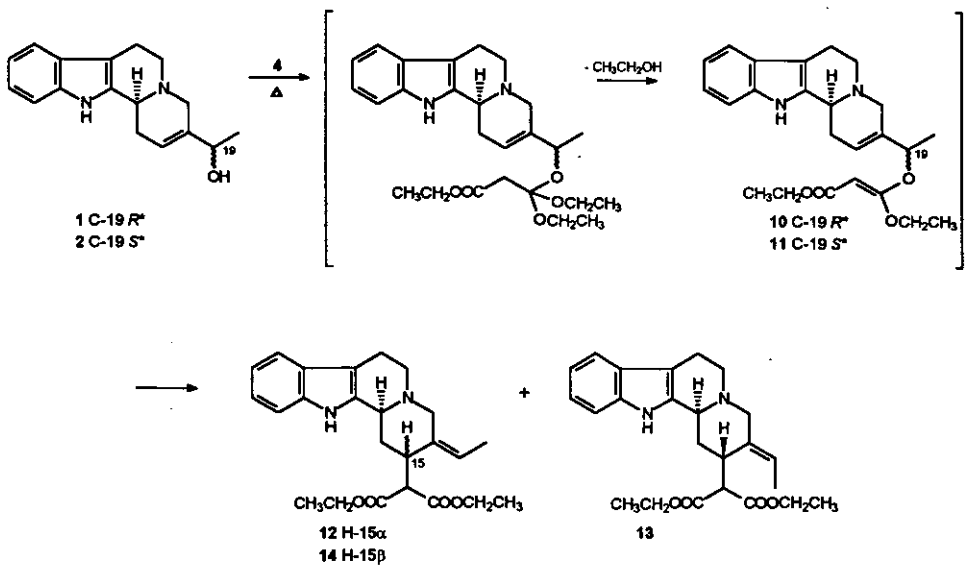
6 R= CH_3CH_2-
7 R= CH_3-

8 R= CH_3CH_2-
9 R= CH_3-

4 R= CH_3CH_2-
5 R= CH_3-

Scheme 1.

Heating the mixture of allylic alcohol (**1**) or (**2**), and triethyl ortho-2-ethoxycarbonylacetate (**4**) in dry dioxane (or in dry toluene; see Experimental) afforded, *via* vinyl allyl ethers (**10**) and (**11**), respectively, deplancheine derivatives (**12**) and (**13**) together, or (**14**) alone (Scheme 2).[15,16]



1 C-19 *R**
2 C-19 *S**

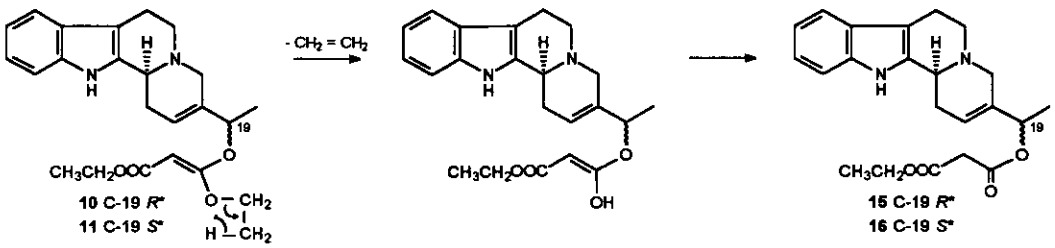
10 C-19 *R**
11 C-19 *S**

12 H-15α
14 H-15β

13

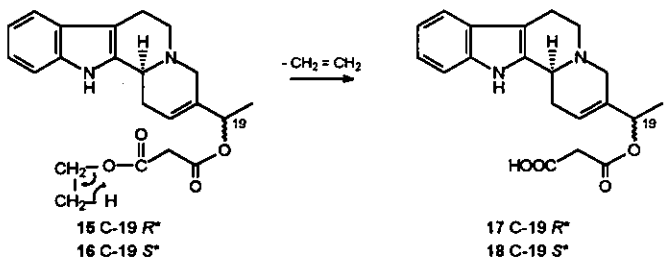
Scheme 2.

However, due to competitive elimination of ethylene from intermediates (**10**) and (**11**), compounds (**15**) and (**16**) were also formed (Scheme 3).



Scheme 3.

Moreover, when toluene was used as solvent (see Experimental), ethylene was to some extent eliminated from compounds (**15**) and (**16**), leading to compounds (**17**) (traces) and (**18**) (Scheme 4).



Scheme 4.

The ^{1}H- and ^{13}C-nmr data of the products formed (See Experimental and Figure 1), taking into account our earlier results and conformational considerations,[7,17-20] are in good agreement with the proposed structures.

CONCLUSIONS

We have been able to prepare in one step, from the easily accessible allylic alcohols (**1**) and (**2**), and the orthoester derivative (**4**) of malonic acid, the 15-malonyldeplancheines (**12**), (**13**) and (**14**), which represent versatile synthetic intermediates[21] for the preparation of *Corynanthé* alkaloids and similar structures.

As far as we know, this is the first time that an orthoester of malonic acid has been successfully used in a Claisen orthoester rearrangement.

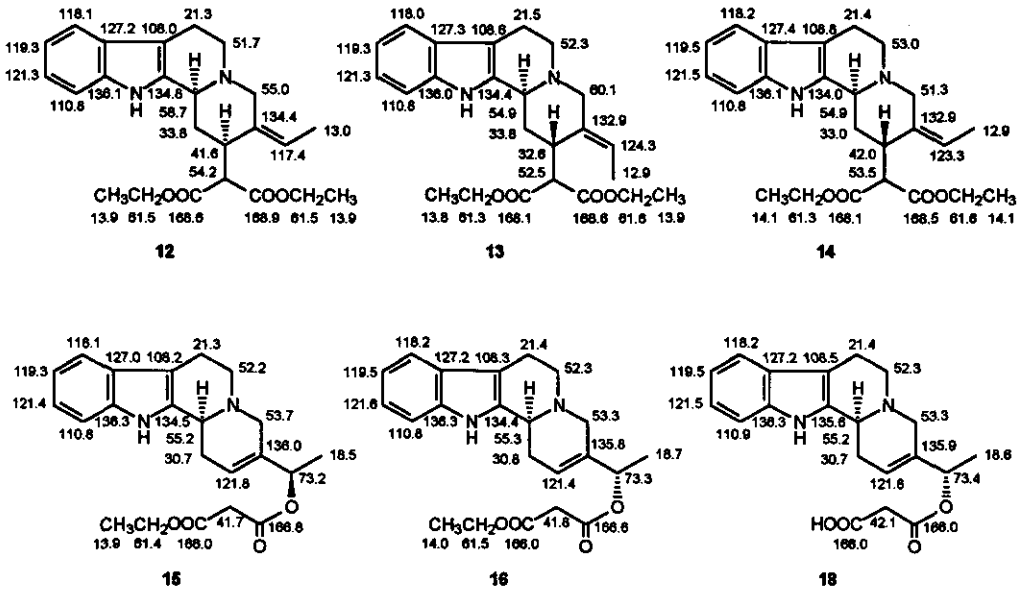


Figure 1. ^{13}C-Nmr data of compounds (**12 - 16**) and (**18**).

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer with $CHCl_3$ used as solvent. Ir absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^{1}H- and ^{13}C-nmr spectra were measured in $CDCl_3$ either with a Varian Gemini-200 spectrometer working at 199.975 MHz (^{1}H-nmr) and 50.289 MHz (^{13}C-nmr) or with a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^{1}H-nmr) and 100.577 MHz (^{13}C-nmr). Chemical shifts are given in ppm by reference to TMS (^{1}H-nmr; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-nmr; δ_C=77.00 ppm). Signal assignments were confirmed by APT experiments. Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of triethyl ortho-2-ethoxycarbonylacetate (4) by the "Pinner method".

Dry hydrogen chloride was passed into a cooled (0 °C) solution of 10 ml (94 mmol) of ethyl cyanoacetate (**6**)[13] (dried over calcium chloride and distilled) and 6.6 ml (112 mmol) of ethanol, until an increase in weight of 4.1 g (112 mmol) was obtained. This solution was stored at 10 °C for

1 day, during which time a large amount of imidate hydrochloride crystallized from the solution. The crystals were filtered, washed with ether and dried in vacuo to give 17.4 g imidate hydrochloride (**8**) (89 mmol, 95%).

The imidate hydrochloride (**8**) (5.2 g, 27 mmol) was suspended in dry ethanol (15 ml) and the mixture was stirred at room temperature for 1 day (Ar atm). K_2CO_3 (1.2 g, 8.7 mmol) was added and the mixture was stirred for 10 min. Ethanol was evaporated and the residue was washed with ether, which then was distilled on a waterbath and the residue was distilled to give triethyl ortho-2-ethoxycarbonylacetate (**4**). Y. 3.6 g (57%). Oil. Bp 74-82 °C/2 mm. ^{1}H Nmr: 1.21 (9H, t, J=7 Hz, 3 × -OCH$_2$*CH$_3$*), 1.26 (3H, t, J=7 Hz, -COOCH$_2$*CH$_3$*), 2.83 [2H, s, CH$_3$CH$_2$OOC-*CH$_2$*-C(OCH$_2$CH$_3$)$_3$], 3.61 (8H, q, J=7 Hz, 4 × -O*CH$_2$*CH$_3$). ^{13}C Nmr: 13.9, 14.7, 38.5, 57.6, 60.4, 112.9, 168.2. Ms: 234 (M^+, <1%), 189, 161, 143, 115 (100%). HRms: Calcd for $C_9H_{17}O_4$ ($C_{11}H_{22}O_5$ - C_2H_5O): 189.1126. Found: 189.1126. Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.19; H, 9.32.

Reaction between allylic alcohol (1) and triethyl ortho-2-ethoxycarbonylacetate (4) in 1,4-dioxane.

A solution of allylic alcohol (**1**) (300 mg, 1.22 mmol), triethyl ortho-2-ethoxycarbonylacetate (**4**) (1050 mg, 4.48 mmol, 4 equiv.), and acetic acid (5 μl) in 1,4-dioxane (10 ml, Na dried and distilled) was stirred for 7 days at 100 °C (Ar atm). The solvent was evaporated and the residue was dissolved in CH_2Cl_2. The organic layer was neutralized with saturated $NaHCO_3$ solution, washed with water, and dried with Na_2SO_4. The crude product was purified by flash chromatography (silica gel) to give compounds (**13**) and (**15**) (CH_2Cl_2:MeOH/99.5:0.5) and (**12**) (CH_2Cl_2:MeOH/99.3:0.7). The mixture of compounds (**13**) and (**15**) was further fractionated by repeated plc (silica gel, CH_2Cl_2:MeOH/98:2).

Compound (**12**). Y. 159.5 mg (35%). Amorphous material. Ir: 1725 (2 × C=O). ^{1}H Nmr: 1.27 (6H, t, J=7 Hz, 2 × -OCH$_2$*CH$_3$*), 1.68 (3H, d, J=6 Hz, H-18), 3.53 (1H, br d, J=11 Hz, H-3), 3.84 (1H, d, J=13 Hz, H-21β), 4.22 (4H, q, J=7 Hz, 2 × -COO*CH$_2$*CH$_3$), 5.25 (2H, q, J=6 Hz, H-19), 7.0-7.2 (2H, m, H-10, H-11), 7.27 (1H, d, J=7 Hz, H-12), 7.44 (1H, d, J=7 Hz, H-9), 8.06 (1H, s, NH). Ms: 410 (M^+), 251 (100%), 170, 169. HRms: Calcd for $C_{24}H_{30}N_2O_4$: 410.2206. Found: 410.2209. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70,02; H, 7.24; N, 6.64.

Compound (**13**). Y. 28.1 mg (6%). Amorphous material. Ir: 1725 (2 × C=O). ^{1}H

Nmr: 1.31 (6H, t, J=7 Hz, 2 × $-OCH_2CH_3$), 1.63 (3H, d, J=6 Hz, H-18), 4.15-4.30 (4H, m, 2 × $-COOCH_2CH_3$), 5.56 (2H, q, J=6 Hz, H-19), 7.0-7.2 (2H, m, H-10, H-11), 7.28 (1H, d, J=7 Hz, H-12), 7.48 (1H, d, J=7 Hz, H-9), 7.95 (1H, br s, NH). Ms: 410 (M^+), 251 (100%), 170, 169. HRms: Calcd for $C_{24}H_{30}N_2O_4$: 410.2206. Found: 410.2201. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.08; H, 7.26; N, 6.62.
Compound (**15**). Y. 52.4 mg (12%). Amorphous material. Ir: 1725 (2 × C=O). ^1H Nmr: 1.28 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.38 (3H, d, J=6 Hz, H-18), 3.37 [<2H, s, $-CO-CH_2-CO-$ (partly enolized)], 4.21 (2H, q, J=7 Hz, $-COOCH_2CH_3$), 5.40 (2H, q, J=6 Hz, H-19), 5.84 (1H, br, H-15), 7.0-7.2 (2H, m, H-10, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.48 (1H, d, J=7 Hz, H-9), 8.12 (1H, s, NH). Ms: 382 (M^+), 251 (100%), 170, 169. HRms: Calcd for $C_{22}H_{26}N_2O_4$: 382.1893. Found: 382.1910. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.18; H, 6.68; N, 7.18.

Reaction between allylic alcohol (1) and triethyl ortho-2-ethoxycarbonylacetate (4) in toluene.
A solution of allylic alcohol (**1**) (113 mg, 0.42 mmol), triethyl ortho-2-ethoxycarbonylacetate (**4**) (520 mg, 2.22 mmol, 5 equiv.), and acetic acid (5 μl) in toluene (13 ml, Na dried and distilled) was stirred for 3 days at 111 °C (Ar atm). The solvent was evaporated, the residue was dissolved in CH_2Cl_2 and the solution was neutralized with solid $NaHCO_3$. The crude product was purified by flash chromatography (silica gel) to give compounds (**13**) and (**15**) (CH_2Cl_2:MeOH/99.5:0.5), (**12**) (CH_2Cl_2:MeOH/99.3:0.7), and (**17**) (CH_2Cl_2:MeOH/99:1). The mixture of compounds (**13**) and (**15**) was further fractionated by repeated plc (silica gel, CH_2Cl_2:MeOH/98:2).
Compound (**12**). Y. 40.3 mg (23%). For the analytical data, see above.
Compound (**13**). Y. 11.6 mg (7%). For the analytical data, see above.
Compound (**15**). Y. 32.4 mg (20%). For the analytical data, see above.
Compound (**17**). Traces. Ms: 354 (M^+, <2%), 310, 251, 170 (100%), 169.

Reaction between allylic alcohol (2) and triethyl ortho-2-ethoxycarbonylacetate (4) in 1,4-dioxane.
A solution of allylic alcohol (**2**) (114 mg, 0.43 mmol), triethyl ortho-2-ethoxycarbonylacetate (**4**) (503 mg, 2.15 mmol, 5 equiv.), and acetic acid (5 μl) in 1,4-dioxane (10 ml, Na dried and distilled) was stirred for 7 days at 100 °C (Ar atm). The solvent was evaporated and the residue was dissolved in CH_2Cl_2. The organic layer was neutralized with a saturated

$NaHCO_3$ solution, washed with water, and dried with Na_2SO_4. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2:MeOH/99.5:0.5) to give a mixture of compounds (**14**) and (**16**). The mixture of compounds (**14**) and (**16**) was further fractionated by repeated plc (silica gel, CH_2Cl_2:MeOH/98:2).

Compound (**14**). Y. 40.3 mg (23%). Amorphous material. Ir: 1720 (2 × C=O). ^{1}H Nmr: 1.25 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.33 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.66 (3H, d, J=7 Hz, H-18), 3.92 (1H, d, J=12 Hz, H-21β), 4.14 (2H, q, J=7 Hz, $-COOCH_2CH_3$), 4.30 (2H, q, J=7 Hz, $-COOCH_2CH_3$), 5.49 (2H, q, J=7 Hz, H-19), 7.0-7.2 (2H, m, H-10, H-11), 7.29 (1H, d, J=7 Hz, H-12), 7.47 (1H, d, J=7 Hz, H-9), 7.74 (1H, br s, NH). Ms: 410 (M^+), 251 (100%), 170, 169. HRms: Calcd for $C_{24}H_{30}N_2O_4$: 410.2206. Found: 410.2193. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.08; H, 7.24; N, 6.68.

Compound (**16**). Y. 37.8 mg (23%). Amorphous material. Ir: 1725 (2 × C=O). ^{1}H Nmr: 1.29 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.42 (3H, d, J=6 Hz, H-18), 3.38 [<2H, s, $-CO-CH_2-CO-$ (partly enolized)], 4.22 (2H, q, J=7 Hz, $-COOCH_2CH_3$), 5.45 (2H, q, J=6 Hz, H-19), 5.87 (1H, br, H-15), 7.0-7.2 (2H, m, H-10, H-11), 7.33 (1H, d, J=7 Hz, H-12), 7.50 (1H, d, J=7 Hz, H-9), 7.80 (1H, br s, NH). Ms: 382 (M^+), 251 (100%), 170, 169. HRms: Calcd for $C_{22}H_{26}N_2O_4$: 382.1893. Found: 382.1864. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.89; H, 6.76; N, 7.18.

Reaction between allylic alcohol (2) and triethyl ortho-2-ethoxycarbonylacetate (4) in toluene.

A solution of allylic alcohol (**2**) (114 mg, 0.43 mmol), triethyl ortho-2-ethoxycarbonylacetate (**4**) (498 mg, 2.13 mmol, 5 equiv.), and acetic acid (5 μl) in toluene (13 ml, Na dried and distilled) was stirred for 3 days at 111 °C (Ar atm). The solvent was evaporated, the residue was dissolved in CH_2Cl_2 and the solution was neutralized with solid $NaHCO_3$. The crude product was fractionated by flash chromatography (silica gel) to give a mixture of compounds (**14**) and (**16**) (CH_2Cl_2:MeOH/99.5:0.5), and compound (**18**) (CH_2Cl_2:MeOH/99:1). The mixture of compounds (**14**) and (**16**) was further fractionated by repeated plc (silica gel, CH_2Cl_2:MeOH/98:2).

Compound (**14**). Y. 32.5 mg (19%). For the analytical data, see above.

Compound (**16**). Y. 30.2 mg (19%). For the analytical data, see above.

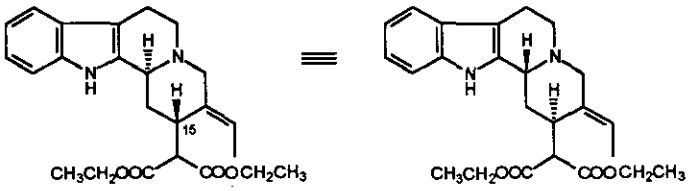
Compound (**18**). Y. 22.2 mg (15%). Amorphous material. Ir: 1725 (2 × C=O). ^{1}H Nmr: 1.42 (3H, d, J=6 Hz, H-18), 3.41 [<2H, s, $-CO-CH_2-CO-$ (partly enolized)], 5.45 (2H, q, J=6 Hz, H-19), 5.85 (1H, br, H-15), 7.0-7.2 (2H,

m, H-10, H-11), 7.25 (1H, d, J=7 Hz, H-12), 7.49 (1H, d, J=7 Hz, H-9), 7.71 (1H, s, NH). Ms: 354 (M^+, <2%), 310, 251, 170 (100%), 169. HRms: Calcd for $C_{19}H_{22}N_2O_2$ ($C_{20}H_{22}N_2O_4$ - CO_2): 310.1681. Found: 310.1688. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.58; H, 6.32; N, 7.96.

REFERENCES AND NOTES

1. S. J. Rhoads and N. R. Raulins, "Organic Reactions", Vol. 22, ed. by W. G. Dauben, Wiley, New York, 1975, pp. 1-74.
2. G. B. Bennett, *Synthesis*, 1977, 589.
3. S. Blechert, *Synthesis*, 1989, 71.
4. F. E. Ziegler, *Acc. Chem. Res.*, 1977, **10**, 227.
5. J. Seyden-Penne, "Synthèse et Catalyse Asymétriques", InterÉditions/ CNRS Éditions, Paris, 1994, pp. 464-470.
6. M. Lounasmaa, R. Jokela, B. Tirkkonen, J. Miettinen, and M. Halonen, *Heterocycles*, 1992, **34**, 321.
7. P. Hanhinen, T. Nurminen, R. Jokela, and M. Lounasmaa, *Heterocycles*, 1994, **38**, 2027.
8. M. Lounasmaa, P. Hanhinen, and R. Jokela, *Tetrahedron*, 1995, **51**, 8623.
9. Biogenetic numbering. J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
10. M. Lounasmaa and A. Tolvanen, "The Monoterpenoid Indole Alkaloids", ed. by J. E. Saxton, 2nd Ed., Wiley, New York, 1994, pp. 57-159.
11. A. Pinner, *Ber.* 1883, **16**, 352 and 1643. See also, R. H. DeWolfe, *Synthesis*, 1974, 153.
12. S. M. McElvain and J. P. Schroeder, *J. Am. Chem. Soc.*, 1949, **71**, 40.
13. Aldrich, Compound 24,120-2.
14. Aldrich, Compound 10,842-1.
15. In conformity with our general presentation of the indoloquinolizidines under examination, compounds (**1** - **2**), (**10** - **11**), and (**15** - **18**) are drawn in such a way that their relative configurations become 3*S**,19*R** and 3*S**,19*S**, respectively. This is done despite the convention that the centre of chirality, which is first cited and which has the lowest locant, generally is presented in such a way that its chirality descriptor becomes *R**. "A Guide to IUPAC Nomenclature of Organic Compounds", Recommendations 1993, ed. by R. Panico, W. H. Powell, and J.-C. Richer, Blackwell Scientific Publications, Oxford, 1993, p. 154.

16. Racemic compound (**13**) is identical with racemic compound (**13'**). Since compound (**13**) is formed by the Claisen rearrangement from the vinyl allyl ether (**10**), for mechanistic reasons we prefer its presentation as shown, even though the C-15-H in formula (**13**), being β, is unnatural.



13 ≡ **13'**

Likewise, the same situation holds for compound (**14**).

17. R. Jokela, M. Halonen, and M. Lounasmaa, *Tetrahedron*, 1993, **49**, 2567.
18. M. Lounasmaa, R. Jokela, P. Hanhinen, J. Miettinen, and J. Salo, *Tetrahedron*, 1994, **50**, 9207.
19. M. Lounasmaa, R. Jokela, P. Hanhinen, J. Miettinen, and J. Salo, *J. Nat. Prod.*, 1995, **58**, 131.
20. M. Lounasmaa, R. Jokela, M. Bäck, P. Hanhinen, and C. Laine, *Tetrahedron*, 1995, **51**, 11891. **Note!** The C-19 assignments (*R* v. S**) of compounds **1** (**1a**, **1b**) - **2** (**2a**, **2b**) are erroneous and should be interchanged.
21. We have recently shown that different C-15 substituted *Z*-deplancheines can easily be transformed to the corresponding *E*-deplancheines.[18,19,22-24]
22. M. Lounasmaa, R. Jokela, J. Miettinen, and M. Halonen, *Heterocycles*, 1992, **34**, 1497.
23. M. Lounasmaa, R. Jokela, M. Halonen, and J. Miettinen, *Heterocycles*, 1993, **36**, 2523.
24. M. Lounasmaa, R. Jokela, U. Anttila, P. Hanhinen, and C. Laine, *Tetrahedron*, 1996, **52**, 6803.

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