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ATROP-DIASTEREOMER SEPARATION BY RACEMATE RESOLUTION TECHNIQUES: *N*-METHYL-DIONCOPHYLLINE A AND ITS 7-EPIMER FROM *ANCISTROCLADUS ABBREVIATUS**

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Key Word Index—*Ancistrocladus abbreviatus*; Ancistrocladaceae; stem bark; naphthyl isoquinoline alkaloids; *N*-methyl-dioncophylline A; chemotaxonomy.

Abstract—The isolation of *N*-methyl-dioncophylline A and *N*-methyl-7-*epi*-dioncophylline A from *Ancistrocladus abbreviatus* is described. Atrop-diastereomer resolution was achieved analytically on a chiral chromatographic phase, and preparatively after esterification with a chiral carboxylic acid. Structural elucidation assisted by partial synthesis is reported and chemotaxonomic implications of this first isolation of Dioncophyllaceae alkaloids from an *Ancistrocladus* species are discussed.

INTRODUCTION

Several species of the tropical plant genus *Ancistrocladus* [3] have been found to produce naphthyl isoquinoline alkaloids [4], structurally intriguing biaryl compounds, such as ancistrocladine (**1**) [5], "the most unusual of all the isoquinoline alkaloids" [6], and ancistrocladisine (**2**) [7]. Despite variations concerning the position of the biaryl linkage, the degree of hydrogenation in the heterocyclic isoquinoline ring, and degree of *O*-methylation, all the *Ancistrocladus* alkaloids that have been fully elucidated structurally so far, have *S*-configuration at C-3 and an oxygen function at C-6. In this respect, they differ significantly from the related Dioncophyllaceae alkaloids, such as dioncophylline A (**3a**) [8, 9], which have 3*R*-configuration and lack the oxygen function at C-6.

No chemical work has been done so far on the West African shrub *Ancistrocladus abbreviatus* Airy Shaw. We now report the first isolation and structure elucidation of *N*-methyl-dioncophylline A (**4a**) and its atrop-diastereomer **4b**, i.e. novel Dioncophyllaceae alkaloids, from this *Ancistrocladus* species. This work has been reported in a preliminary form [2].

RESULTS AND DISCUSSION

Air-dried and ground stem bark of *A. abbreviatus* from West Ivory Coast was extracted successively with petrol, CH_2Cl_2 and EtOH. The red residue (EtOH) was chromatographed on Al_2O_3 with $CH_2Cl_2 \rightarrow CH_2Cl_2$–MeOH (9:1). Purification by crystallization from acetone afforded 420 mg (*ca* 0.025%) crystals, which appeared homogeneous by TLC. The spectroscopic data closely resembled those of dioncophylline A (**3a**), but with an NMR signal for an additional *N*-methyl group. Beyond the constitution, the relative configuration at the stereogenic centres C-1 and C-3 was established to be *trans* by comparison of the H-3 signal (δ 3.30) with the corresponding signals of related naphthyl isoquinolines [8].

A more detailed analysis of the ^{1}H NMR spectrum however revealed that the isolated product occurred as a diastereomeric mixture (**4x/y**), as indicated by the fact that many signals were slightly split, the singlets for Me-2′ and OH-8 being suitable for a determination of the ratio **4x/y** as *ca* 1:1. In consequence, the isolated crystalline compound had to be a mixture of two diastereomeric *N*-methyl-dioncophyllines A, both with *trans* configuration at C-1 and C-3, i.e. **4a/b**, **4a/c**, **4b/d** or **4c/d**.

Recently, we have developed a first synthetic pathway to Ancistrocladaceae and Dioncophyllaceae alkaloids [10–13], e.g. to dioncophylline A (**3a**) and its isomers **3c** and **3d** [9]. For the preparation of authentic samples of selected stereoisomers of **4**, the synthetic dioncophyllines A **3a** and **3c** were *N*-methylated (Scheme 1) to give **4a** and **4c** respectively. By ^{1}H NMR comparison of the pure compounds as well as by directed separate addition of **4a** or **4c** to the isolated mixture, the identity of **4x** with **4a** (or its enantiomer **4d**) and **4y** with **4c** (or its enantiomer **4b**) was established.

Chromatographic separation of **4x/y** proved to be extremely difficult. Fractional crystallization led to unsatisfactory *ca* 1:1 proportions of **4x/4y**. Also TLC and HPLC, using a wide variety of solvent/adsorbent systems, failed to give resolution of the diastereomeric alkaloids **4x/y**, because these behaved almost like enantiomers. Consequently, racemate resolution procedures were applied to the separation of **4x/y**. With the reference compounds **4a** and **4c** in hands, HPLC on the chiral

*Part 20 in the series 'Acetogenic Isoquinoline Alkaloids'. For Parts 18 and 19, see refs [1, 2].

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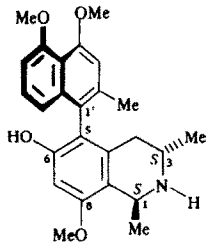
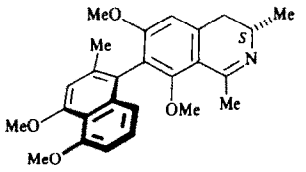


1



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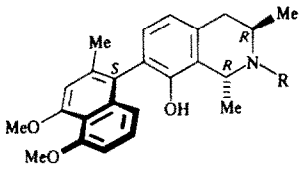
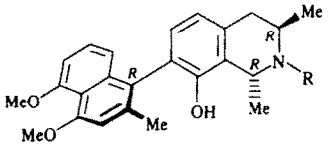
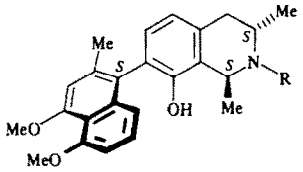


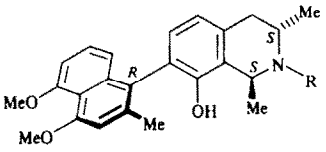
3a
4a



3b **3a-d** **4a-d**
4b R H Me



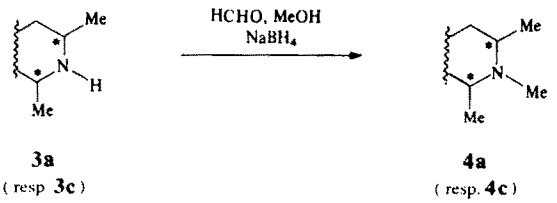
3c = *ent*-**3b**
4c = *ent*-**4b**



3d = *ent*-**3a**
4d = *ent*-**4a**

adsorbent 'chiralcel OD' (Daicel Chemical Industries Ltd), using *iso*-propanol–*n*-hexane (1:9) as eluent (see Experimental), was found to be an efficient analytic device, clearly discriminating between the different stereoisomers.

This analytic procedure showed that **4x** (R_t 19.0 min) was identical to **4a**—with the remaining insecurity that the chromatographic behaviour of **4d** was not known. Compound **4y** (R_t 16.1 min) was clearly different from **4c** (R_t 20.9 min) and hence should be **4b**. Interestingly, the enantiomers **4b** and **4c** gave a better chromatographic differentiation than the corresponding diastereomers.



3a
(resp. **3c**)

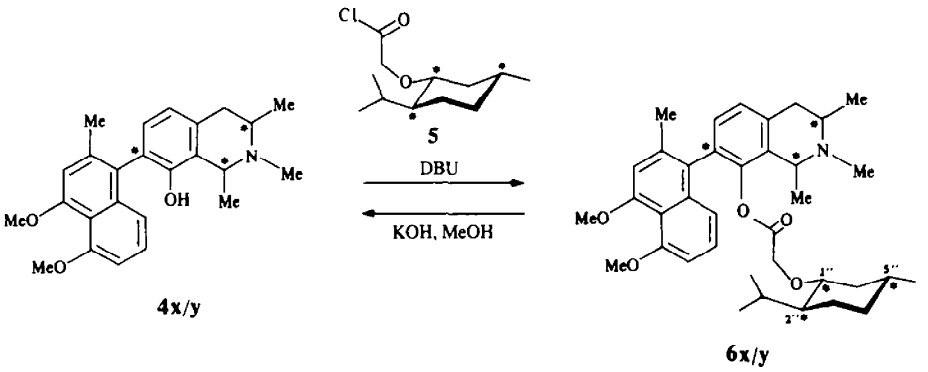
4a
(resp. **4c**)

Scheme 1. *N*-Methylation of dioncophylline A stereoisomers

For a preparative separation of **4x** and **4y**, their insufficient diastereomeric character was enhanced by esterification of the free phenolic function at C-8 with an optically active chiral carboxylic acid. The best results were obtained using the chloride **5** of (−)-menthoxyacetic acid as a chiral auxiliary (Scheme 2), which due to the oxyacetate spacer is 'slim' enough to reach the 8-oxygen function and is sterically differentiated enough to allow an efficient chromatographic separation.

The resulting menthoxyacetates **6x/y** were separable, e.g. on MPLC-silica gel (CH_2Cl_2–MeOH–NEt_3, 1990:10:1). Subsequent ester saponification of the stereochemically homogeneous esters **6x** and **6y** was performed in methanolic KOH, leading to the pure alkaloids **4x** and **4y**. Comparison of the spectroscopic and chiroptical data of the isolated alkaloids **4x** and **4y** with those of the synthetic samples **4a** and **4c** allowed an unequivocal structural attribution to the natural products isolated. Accordingly, the alkaloid **4x** arising from the chromatographically slower ester **6x** is identical with *N*-methyldioncophylline A (**4a**) and the alkaloid **4y**, as obtained by cleavage of the ester **6y**, is **4b**, i.e. *N*-methyl-7-*epi*-dioncophylline A.

This isolation and identification of **4a** and **4b** is of great stereochemical, biosynthetic, and phylogenetic interest:



Scheme 2. Derivatization of **4x/y** to give **6x/y**, and cleavage subsequent to chromatographic resolution.

whereas **4a** is just the *N*-methylated form* of the known [8, 9] Dioncophyllaceae alkaloid dioncophylline A, **4b** is the first representative of a Dioncophyllaceae alkaloid with *R*-configuration at the biaryl axis. All other alkaloids of this type isolated so far, were found to be atropoisomerically homogeneous and had *S*-configuration with respect to rotational isomerism.

More strikingly however, this work represents the first isolation of Dioncophyllaceae alkaloids (i.e. with the typical 3*R*-configuration and lacking a 6-oxygen function) from an *Ancistrocladus* species, thus clearly violating the hitherto strict differentiation between these two classes of naphthyl isoquinoline alkaloids. This finding suggests that *A. abbreviatus*, from its chemotaxonomical behaviour, may be considered as a phylogenetic link between the Ancistrocladaceae and the Dioncophyllaceae. Further work to support this assumption is in progress.

EXPERIMENTAL

General. Mps: uncorr; Optical rotations: 20° or 25°, 10 cm cell, $CHCl_3$ (filtered through basic Al_2O_3); CD: 20°, EtOH; IR: KBr; ^1H NMR (200 or 400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ with TMS as int. standard; MS: 70 eV. Analyses (C, H and N) were performed by the Department of Inorganic Chemistry, University of Würzburg. CC: Neutral Al_2O_3 (Woelm) was modified with 6% H_2O (i.e. 'activity III'), silica gel (60–200 mesh, Merck) by addition of 7.5% aq. NH_3. TLC: precoated silica gel 60 F_{254} plates (Merck), deactivated with NH_3; spots were visualized under UV and by Dragendorff's reagent.

Plant material. Stem bark of *Ancistrocladus abbreviatus* Airy Shaw was collected in the West Ivory Coast in January 1988 and identified by one of us (L. Aké Assi). A voucher specimen is deposited at his herbarium, Conservatoire et Jardin Botaniques de l'Université d'Abidjan, République de Côte d'Ivoire.

Extraction and isolation. Freeze-dried and ground stem bark (*ca* 2 kg) was macerated with petrol, CH_2Cl_2 and EtOH, assisted by ultrasound. Solvents were evapd under red. pres. and the crude EtOH extract (196 g) was filtered through neutral Al_2O_3. On TLC, the CH_2Cl_2–MeOH (9:1) filtrate contained a mixt. of at least 7 different alkaloids. The soln was evapd and the residue (15.2 g) was subjected to CC on 225 g neutral Al_2O_3. The column was eluted with mixts of petrol–CH_2Cl_2–MeOH of increasing polarity. The CH_2Cl_2 soln exhibited a single band on TLC, it was evapd, and crystallization of the residue from Me_2CO yielded 420 mg (*ca* 0.025%) of **4a, b** ('**4x**, y'). When repeating the isolation procedure with CC on silica gel, 320 mg (0.064%) **4a, b** were obtained from 500 g plant material. The ^1H NMR spectrum of the isolated product revealed a *ca* 1:1 mixt. of diastereomers, which had to be further resolved.

Menthoxy-acetylation of **4a, b** *and preparative atrop-diastereomer separation.* A soln of **4a, b** (101 mg) and 1.5 eq **5** [prepared from (−)-menthoxy acetic acid (Fluka) and $SOCl_2$] in 10 ml CH_2Cl_2 was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (39.4 mg). After stirring at room temp. for 1 hr, the reaction mixt. was filtered to remove DBU·HCl, evapd and chromatographed on neutral Al_2O_3 with CH_2Cl_2 to yield an amorphous solid (127 mg). Repeated CC of 300 mg **6a, b** on silica gel (15–25 mesh) with CH_2Cl_2–MeOH–NEt_3 (1990:10:1) afforded **6a** (56 mg) and **6b** (118 mg).

8-Menthoxyacetyl-N-methyldioncophylline A (**6a**). $[\alpha]_D^{25}$ +4.9° ($CHCl_3$; *c* 0.27). IR ν_{max}^{KBr} cm^{-1}: 2950, 2920, 2860, 2840, (C–H), 1770 (C=O), 1580 (C=C), 1390 (C–H), 1260 (C–O); ^1H NMR (200 MHz); δ 0.57 (3H, *d*, *J* = 6.9 Hz, Me-5''), 0.79 [6H, *d*, *J* = 7 Hz, $CH(Me)_2$], 0.6–0.9 (2H, complex), 0.9–1.15 (2H, complex), 1.24 (3H, *d*, *J* = 6.2 Hz, Me-1), 1.30 (3H, *d*, *J* = 6.8 Hz, Me-3), 1.4–1.7 (4H, complex), 2.05 [1H, *septd*, J_1 = 7 Hz, J_2 = 2.3 Hz, $CH(Me)_2$], 2.17 (3H, *s*, Me-2'), 2.34 (1H, *td*, J_{ax} = 10.5 Hz, J_{eq} = 3 Hz, 1''-H), 2.38 (3H, *s*, N-Me), 2.71–2.75 (2H, *m*, 4-H_{ax}, 4-H_{aq}), 3.35 (1H, m_C, 3-H), 3.40 (1H, *d*, *J* = 17.2 Hz, O–CH_2–CO_2), 3.58 (1H, *d*, *J* = 17.2 Hz, O–CH_2–CO_2), 3.92; 3.94 (each 3H, *s*, OMe), 3.94 (1H, *q*, *J* = 6.2 Hz, H-1), 6.70 (1H, *s*, H-3'), 6.73; 6.89 [each 1H, *dd*, J_1 = 7.6 Hz (8.4 Hz), J_2 = 1 Hz, H-6', H-8'], 7.00; 7.06 (each 1H, *d*, *J* = 7.9 Hz, H-5, H-6), 7.17 (1H, *dd*, J_1 = 7.6 Hz, J_2 = 8.4 Hz, H-7'); MS *m/z* (rel. int.): 587 $[M]^+$ (7), 572 $[M-Me]^+$ (64), 376 $[M-Me-C_{12}H_{20}O_2]^+$ (85). Found: C, 75.21; H, 8.51; N, 2.17. $C_{37}H_{49}NO_5$ requires: C, 75.60; H, 8.40; N, 2.34%).

8-Menthoxyacetyl-N-methyl-7-epi-dioncophylline A (**6b**). $[\alpha]_D^{25}$ −87.2° ($CHCl_3$; *c* 0.74). IR ν_{max}^{KBr} cm^{-1}: 2950, 2920, 2860, 2840 (C–H), 1770 (C=O), 1580 (C=C), 1390 (C–H), 1260 (C–O); ^1H NMR (200 MHz): δ 0.45 (3H, *d*, *J* = 6.9 Hz, Me-5''), 0.6–0.9 (2H, complex), 0.75 [3H, *d*, *J* = 7 Hz, $CH(Me)_2$], 0.87 [3H, *d*, *J* = 7 Hz, $CH(Me)_2$], 0.9–1.15 (2H, complex), 1.23 (3H, *d*, *J* = 6.5 Hz, Me-1), 1.34 (3H, *d*, *J* = 6.8 Hz, Me-3), 1.4–1.7 (4H,

*In principle, the constitution of **4a** corresponds to '*N*-methyltriphyophylline' [14], exhibiting, however, a different optical rotation. Due to further incomplete and incorrect structure elucidation in this series of natural products, the parent compound 'triphyophylline' had to be renamed 'dioncophylline A' [8, 15].

complex), 2.0 [1H, *septd*, $J_1 = 7$ Hz, $J_2 = 2.3$ Hz, $CH(Me)_2$], 2.12 (3H, *s*, Me-2'), 2.35 (3H, *s*, N-Me), 2.45 (1H, *td*, $J_{ax} = 10$ Hz, $J_{eq} = 4$ Hz, H-1''), 2.7–2.74 (2H, *m*, H_{ax}-4, H_{eq}-4), 3.40 (1H, m_C, H-3), 3.45 (1H, *d*, $J = 17$ Hz, O–CH_2–CO_2), 3.72 (1H, *d*, $J = 17$ Hz, O–CH_2–CO_2), 3.84 (1H, *q*, $J = 6.5$ Hz, H-1), 3.93; 3.95 (each 3H, *s*, OMe), 6.69 (1H, *s*, H-3'), 6.75; 6.91 [each 1H, *dd*, $J_1 = 7.5$ Hz (8.5 Hz), $J_2 = 1$ Hz, H-6', H-8'], 7.00; 7.06 (each 1H, *d*, $J = 7.8$ Hz, H-5, H-6), 7.19 (1H, *dd*, $J_1 = 7.5$ Hz, $J_2 = 8.5$ Hz, H-7'); MS *m/z* (rel. int.): 587 $[M]^+$ (10), 572 $[M-Me]^+$ (94), 376 $[M-Me-C_{12}H_{20}O_2]^+$ (100). Found: C, 75.24; H, 8.53; N, 2.23. $C_{37}H_{49}NO_5$ requires: C, 75.60; H, 8.40; N, 2.34%).

Saponification of **6a**. A soln of **6a** (56 mg) in CH_2Cl_2 (10 ml) and 0.05 M methanolic KOH (4.5 ml) was warmed up to 39° for 3 hr. The reaction mixt. was evapd, the residue was extd (× 3) with CH_2Cl_2. The CH_2Cl_2 phases were evapd and the crude product **4a** was chromatographed on silica gel with CH_2Cl_2–MeOH (99:1) yielding 34 mg *N*-methyl-dioncophylline A (**4a**). Crystallization from Me_2CO afforded needles, mp 193°. $[\alpha]_D^{25}$ +15.0° ($CHCl_3$; *c* 1.27)* CD: $\Delta\varepsilon_{210} - 10$, $\Delta\varepsilon_{235} + 19$, $\Delta\varepsilon_{278} + 7$. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), 2960, 2920, 2850 (C–H), 1610, 1580 (C=C), 1380 (C–H), 1260 (C–O); ^1H NMR (200 MHz): δ 1.23 (3H, *d*, $J = 6.4$ Hz, Me-3), 1.35 (3H, *d*, $J = 6.6$ Hz, Me-1), 2.19 (3H, *s*, Me-2'), 2.43 (3H, *s*, N-Me), 2.69–2.73 (2H, *m*, H_{ax}-4, H_{eq}-4), 3.30 (1H, m_C, H-3), 3.90; 3.94 (each, 3H, *s*, OMe), 4.18 (1H, *q*, $J = 6.6$ Hz, H-1), 4.88 (1H, *s*, OH-8), 6.72; 6.94 (each 1H, *dd*, $J_1 = 8$ Hz (8.5 Hz), $J_2 = 1$ Hz, H-6', H-8'), 6.73 (1H, *s*, H-3'), 6.75; 6.82 (each 1H, *d*, $J = 8$ Hz, H-5, H-6), 7.18 (1H, *dd*, $J_1 = 8$ Hz, $J_2 = 8.5$ Hz, H-7'); HPLC: R_t 19.0 min; MS *m/z* (rel. int.): 391 $[M]^+$ (3), 376 $[M-Me]^+$ (100). Found: C, 76.50; H, 7.68; N, 3.46. $C_{25}H_{29}NO_3$ requires: C, 76.70; H, 7.47; N, 3.58%).

Saponification of **6b**. Analogous reaction of **6b** (118 mg) yielded 75 mg *N*-methyl-7-*epi*-dioncophylline A (**4b**). Mp 230°. $[\alpha]_D^{25}$ −6° ($CHCl_3$; *c* 1.12). CD: $\Delta\varepsilon_{210} + 18$, $\Delta\varepsilon_{238} - 19$, $\Delta\varepsilon_{278} - 4$. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), 2960, 2930, 2900 (C–H), 1610, 1580 (C=C), 1380 (C–H), 1260 (C–O); ^1H NMR (400 MHz): δ 1.24 (3H, *d*, $J = 6.4$ Hz, Me-3), 1.36 (3H, *d*, $J = 6.6$ Hz, Me-1), 2.15 (3H, *s*, Me-2'), 2.42 (3H, *s*, N-Me), 2.68 (1H, *dd*, $J_{gem} = 17.0$ Hz, $J_{ax} = 10.5$ Hz, H_{ax}-4), 2.75 (1H, *dd*, $J_{gem} = 17.0$ Hz, $J_{eq} = 5.0$ Hz, H_{eq}-4), 3.30 (1H, m_C, H-3), 3.93 (3H, *s*, OMe-5'), 3.96 (3H, *s*, OMe-4'), 4.19 (1H, *q*, $J = 6.6$ Hz, H-1), 4.78 (1H, *s*, OH-8), 6.73 (1H, *d*, $J = 8.1$ Hz, H-5), 6.75 (1H, *s*, H-3'), 6.75 (1H, *dd*, $J_1 = 8.1$ Hz, $J_2 = 1$ Hz, H-6'), 6.83 (1H, *d*, $J = 8.1$ Hz, H-6), 6.96 (1H, *dd*, $J_1 = 8.5$ Hz, $J_2 = 1$ Hz, H-8'), 7.24 (1H, *dd*, $J_1 = 8.1$ Hz, $J_2 = 8.5$ Hz, H-7'); ^{13}C NMR δ 15.8 (*q*, Me-1), 20.0 (*q*, Me-3), 20.8 (*q*, Me-2'), 34.3 (*t*, C-4), 36.8 (*q*, N-Me), 46.2 (*d*, C-3), 55.5 (*d*, C-1), 56.4 (*q*, OMe-4'), 56.5 (*q*, OMe-5'), 105.8 (*d*, C-6'), 108.8 (*d*, C-3'), 116.4 (*s*), 118.4 (*d*, C-8'), 120.5 (*d*, C-5), 122.5 (*s*), 123.5 (*s*), 126.7 (*s*), 126.9 (*d*, C-7'), 128.5 (*d*, C-6), 134.9 (*s*), 136.9 (*s*), 137.2 (*s*), 149.9 (*s*, C-8), 157.1; 157.3 (*s*, C-4', C-5'); HPLC: R_t 16.1 min; MS *m/z* (rel. int.): 391 $[M]^+$ (2), 376 $[M-Me]^+$ (100). Found: C, 76.59; H, 7.48; N, 3.32. $C_{25}H_{29}NO_3$ requires: C, 76.70; H, 7.47; N, 3.58%).

Partial synthesis of reference compound **4a** *by N-methylation of dioncophylline A* (**3a**). Natural **3a** (70 mg) in MeOH (50 ml) was treated with 40% aq. HCHO (3 ml) at room temp. for 6 hr with stirring. After addn of excess $NaBH_4$, the mixt. was stirred for further 12 hr, acidified with HOAc to pH 4–5, then adjusted to pH 8 with 28% aq. NH_3. The soln was extracted (× 4) with CH_2Cl_2, the CH_2Cl_2 phases evapd and the residue filtered through neutral Al_2O_3 with CH_2Cl_2–MeOH (100:0→24:1). Compound **4a** (68 mg) was crystallized from Me_2CO. The material obtained by partial synthesis was shown to be fully identical with the alkaloid **3a** (mmp, $[\alpha]_D^{25}$, CD IR, ^1H NMR, HPLC).

N-Methylation of 1,3-*bis*-epi-*dioncophylline A* (**3c**). Analogous reaction of **3c** (16 mg), as obtained previously by total synthesis [9], afforded **4c** (15.3 mg), identical with **4b** in all isotropic data (mmp, IR, ^1H NMR). $[\alpha]_D^{20}$ +1.7 ($CHCl_3$; *c* 0.68). CD: $\Delta\varepsilon_{204} - 13$, $\Delta\varepsilon_{234} + 8$, $\Delta\varepsilon_{275} + 2$. HPLC: R_t 20.9 min). Opposite signs of the CD and $[\alpha]_D^{20}$ showed **4c** to be the enantiomer of **4b**.

Analytic separation of N-*methyl-dioncophylline A stereoisomers on a chiral phase*. HPLC analysis was carried out on a Chiralcel OD column (10 μm, 250 mm × 4.6 mm, Daicel Chemical Industries Ltd.) at room temp.; eluent: *n*-hexane–*iso*-PrOH (9:1); flow rate 0.5 ml min^{-1}; detection at 230 nm. After calibration with ref. compounds **4a** and **4c** R_t values were obtained as described above.

Acknowledgements—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Mrs L. Kinzinger and Mrs M. Lehrmann for technical assistance, and Mr M. Rübenacker and Dr J. Jansen for supplying samples of **3a** and **3c**.

*Data for '*N*-methyltriphyophylline': mp 185°, $[\alpha]_D + 70°$ ($CHCl_3$; *c* 1) [14].

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