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Directed Joint Total Synthesis of the three Naphthylisoquinoline Alkaloids Dioncolactone A, Dioncopeltine A, and 5'-*O*-Demethyldioncophylline A[1]

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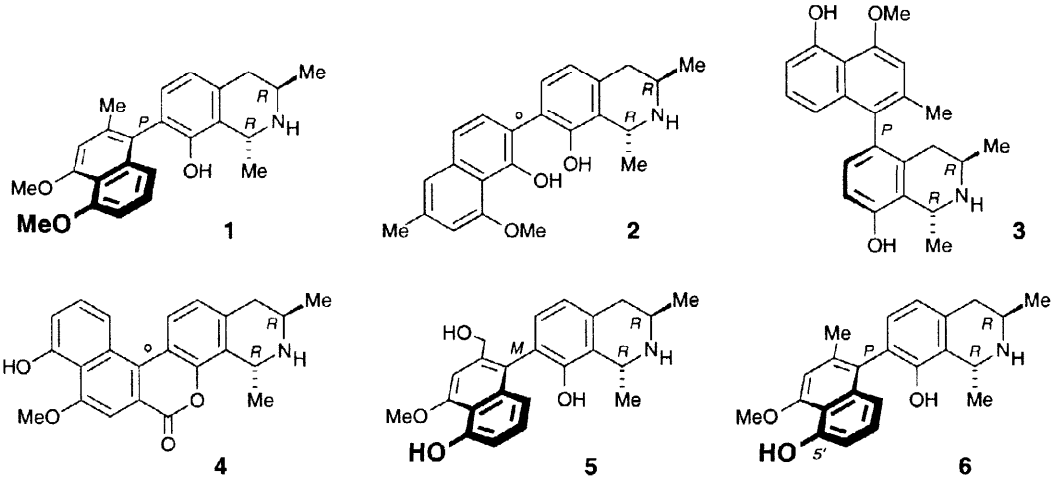
Abstract: The first total synthesis of the three antimalarial naphthylisoquinoline alkaloids dioncolactone A (**4**), dioncopeltine A (**5**), and 5'-*O*-demethyldioncophylline A (**6**) is described. The regio- and stereoselective construction of the biaryl axes was achieved through the 'lactone methodology', by ester-type prefixation of the two molecular moieties, intramolecular coupling, and atropo-diastereoselective cleavage of the lactone auxiliary bridge. As a novel alternative, the configuration at the axis may be installed by atroposelective hydroxy aldehyde reduction through dynamic kinetic resolution.

INTRODUCTION

Triphyophyllum peltatum,[2] a Westafrican liana belonging to the very small Dioncophyllaceae family, is a rich source of naphthylisoquinoline alkaloids, among them dioncophyllines A (**1**), B (**2**), and C (**3**).[3,4] These structurally and biosynthetically unique natural products are characterized by interesting biological activities, which make them attractive synthetic goals.[5-7] Thus, besides other bioactivities (*e.g.* insect growth retarding and antifeedant, as well as fungicidal properties),[8,9] several representatives of this class of alkaloids exhibit high antimalarial activities *in vitro* and *in vivo*.[3,10,11] More detailed structure-activity relationship investigations revealed the antimalarial activity of dioncophylline A (**1**),[12] a rather moderately active representative,



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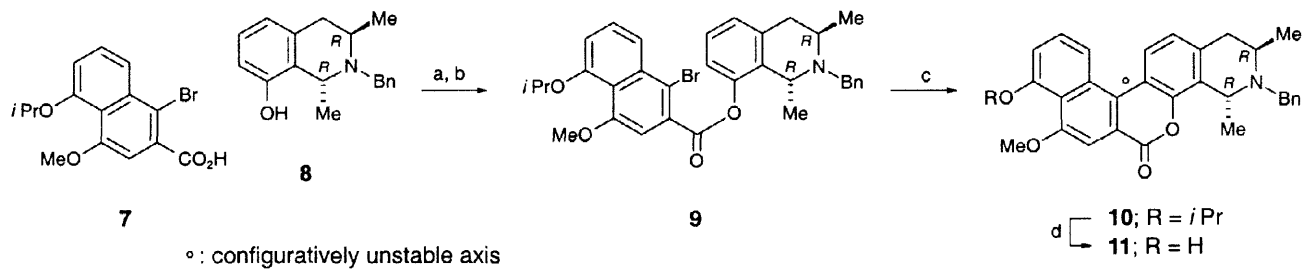
to be distinctly enhanced by the introduction of additional (preferentially free, *i.e.* alcoholic or phenolic) oxygen functions, as exemplified by the increased activities of the three co-ocurring natural products, dioncolactone A (**4**),[13] 5'-*O*-demethyldioncophylline A (**6**),[14] and, in particular, dioncopeltine A (**5**),[11-13] which is, together with dioncophylline C (**3**),[10,11,15] the most active of all the antimalarial naphthylisoquinoline alkaloids. In this paper, we describe the first total synthesis of all of these three alkaloids, **4** – **6**, by a joint and thus very rational synthetic pathway, which takes advantage of the 'lactone methodology'[16,17] and, as an alternative, of the hydroxy aldehyde reduction, efficient methods for the regio- and stereoselective construction of unsymmetrically substituted biaryl axes.

RESULTS AND DISCUSSION

The strategy selected for the synthesis of **6** is related to the synthetic access previously elaborated for the structurally similar main *Triphyophyllum* alkaloid, dioncophylline A (**1**),[5,18] but with the necessity of creating an additional free phenolic OH group in the 5-position of the naphthalene part of **6**. Because of our good experience in the first total syntheses *e.g.* of dioncophylline C (**3**),[7] we chose an isopropyl residue as an appropriate protective group[19,20] for that oxygen function. Within the 'lactone methodology', the creation of the free 8-OH group as well as the introduction of an additional oxygen function in the side chain in **5** should pose no particular problems, since they originate from the reductive lactone opening, anyhow; and **4** as a naturally occurring biaryl lactone happens to fit ideally into our synthetic methodology, since (of course except for the lacking protective groups) it is exactly the type of lactone-bridged biaryl intermediates characteristic of our biaryl synthetic methodology. The total synthesis of **4**, **5**, and **6**, as shown in Schemes 1 and 2, starts with the known[21] enantiomerically pure 1*R*,3*R*-tetrahydroisoquinoline **8** and the *O*-isopropyl protected bromonaphthoic acid **7**, which had already been used in the synthesis of dioncophylline C (**3**).[7] Esterification of the acid chloride of **7** with **8** to give **9** and subsequent intramolecular biaryl coupling with palladium catalysis delivered the lactone **10** in an excellent 92% yield. As expected from related lactone-bridged biaryls,[16,22,23] the biaryl unit of **10** is configuratively unstable, leading to a very rapid interconversion of these two atropodiastereomers. Specific *O*-deprotection using boron trichloride, was best achieved at this level already, leading to **11**.

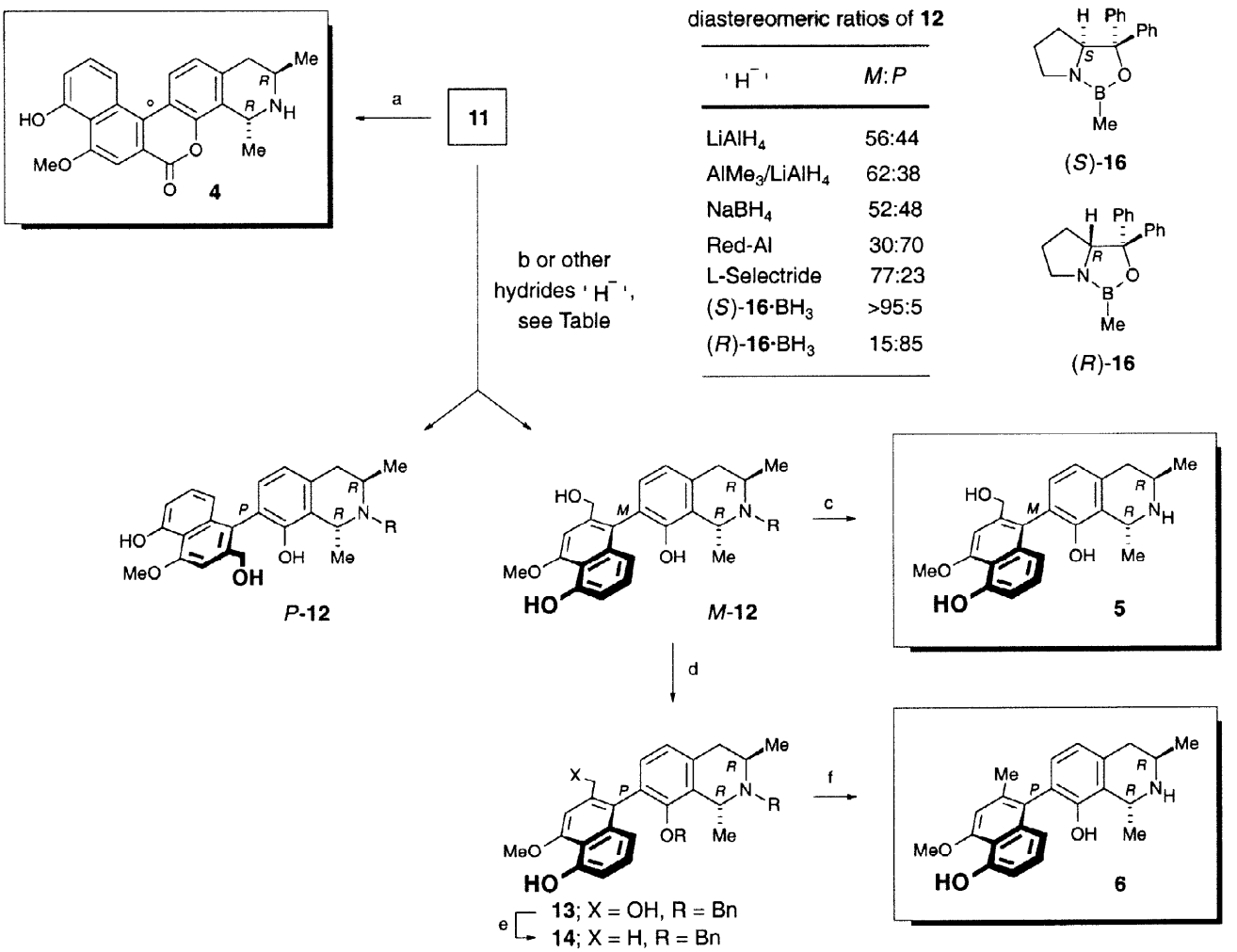


Scheme 1. Reagents and conditions: a) $(COCl)_2$, CH_2Cl_2; b) NEt_3, DMAP, CH_2Cl_2, 85% from **7**; c) $(Ph_3P)_2PdCl_2$, NaOAc, DMA, 100 °C, 92%; d) BCl_3, CH_2Cl_2, -40 °C, 92%.

N-Debenzylation by catalytic hydrogenation (Scheme 2) gave the first of the three natural products, dioncolactone A (**4**), fully identical in all spectroscopic, chromatographic, and physical properties with an authentic sample isolated from *T. peltatum*.[13]

Of the three biaryl lactones thus prepared (**10**, **11**, and **4**), **11** proved to be the best substrate for the continuation of the further synthesis of the other natural target molecules **5** and **6**, given the acid-sensitivity of

the resulting primary benzylic alcohol **12** and the still comfortable polarity of these ring cleavage products because of the *N*-benzyl group. Out a broad variety of different achiral and chiral *H*-transfer reagents, the oxazaborolidine-borane system[24,25] proved to deliver the best asymmetric inductions in the atroposelective cleavage of **11**, leading to *M*-**12** by the use of *S*-oxazaborolidine **16** (>95:5) or, optionally, to *P*-**12** with *R*-**16** as the reagent (15:85). While other, achiral hydrogen transfery agents like $LiAlH_4$ (56:44), $NaBH_4$ (52:48), or $AlMe_3$-$LiAlH_4$ (62:38) gave distinctly worse asymmetric induction, quite good atropisomeric ratios in favor of *M*-**12** were achieved *e.g.* with L-Selectride (77:23), with the advantage of a more rapid reaction, also on a preparative scale. For a recycling of the here undesired atropoisomer, *P*-**12**, see below.



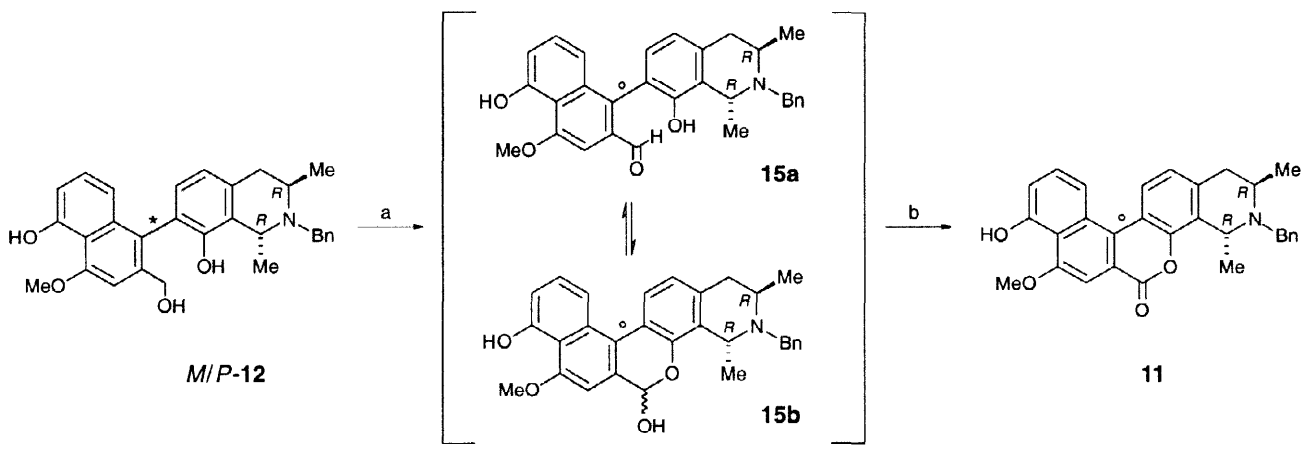
Scheme 2. Completion of the total synthesis of dioncolactone A (**4**), dioncopeltine A (**5**), and 5'-*O*-demethyldioncophylline A (**6**). Reagents and conditions: a) H_2, Pd/C (10%), MeOH, 86%; b) $LiAlH_4$, THF, 0° C, 47%; c) H_2, Pd/C (10%), MeOH, 80%; d) BnBr, Cs_2CO_3, reflux, 96%; e) $(BrCl_2C)_2$, PPh_3, CH_2Cl_2[7,26] → $LiAlH_4$, THF, 0° C, 87%; f) H_2, Pd/C (10%), MeOH, 66%.

The two atropo-diastereomeric primary alcohols, *M*-**12** and *P*-**12** were easily separated by chromatography on silica gel. Cleavage of the *N*-benzyl protective group by hydrogenolysis over Pd/C completed the first total synthesis of dioncopeltine A (**5**), again identical in all respects with natural material previously isolated.[13]

The preparation of the third naphthylisoquinoline alkaloid, 5'-*O*-demethyldioncophylline A (**6**),[14] still required the reductive elimination of the benzylic oxygen function at the naphthalene part of dioncopeltine A

(**5**). Again, this could be done at different levels, the best yields being obtained when first transforming *M*-**12** into **13**, by selectively blocking the 8-oxygen function by *O*-benzylation. Subsequent hydroxy/halogen exchange using the 1,2-dibromotetrachloroethane-PPh_3 system,[7,26] and reduction of the intermediate side chain bromide by $LiAlH_4$ gave **14**, which was deliberated of its *N*-protective group by catalytic hydrogenation, to yield **6**, again fully identical with authentic 5'-*O*-demethyldioncophylline A (**6**) isolated from *T. peltatum*.[14]

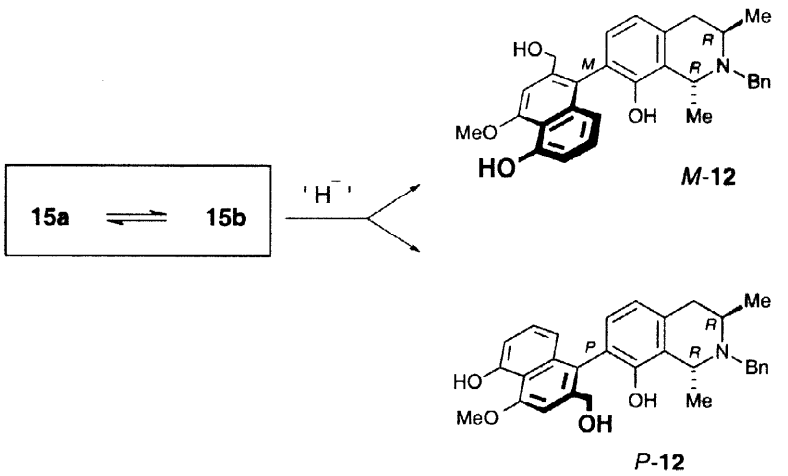
An additional advantage of the lactone methodology is that in principle the undesired minor atropo-diastereomer as possibly likewise formed in such ring cleavage reactions, is not lost if it can be ring-closed again to give the configuratively unstable lactone - a recycling literally by re-cyclization and renewed ring cleavage. While this had already been achieved for biaryl esters as ring cleavage products from *O*-nucleophiles,[22] we here describe the first recycling of biaryl alcohols like **12** as resulting from reductive ring cleavage reactions. Such an oxidation back to **11** was best achieved in two steps: Using pyridinium chlorochromate (PCC) in THF, the hydroxy aldehyde ⇌ lactol equilibrium mixture **15a/15b** was obtained, further diversified by the expected[27-30] interconverting stereoisomeric forms. Subsequent further oxidation with sodium chlorite / NH_2SO_3H (see Scheme 3) gave lactone **11** in a pure form.



Scheme 3. 'Recycling by re-cyclization': stepwise oxidation of *M*- or *P*-**12**. Reagents and conditions: a) PCC, THF, 73%; b) $NaClO_2$, H_2NSO_3H, CH_3CO_2H, dioxan, 65%.

The synthetic availability of the intermediate by hydroxy aldehyde / lactol mixture **15a/15b** in a chemically pure form, *i.e.* free of alcohol **12** or lactone **11**, moreover allowed us to test its atropo-diastereoselective reduction, through dynamic kinetic resolution of the interconverting isomeric species. This methodology had previously been developed for the atropo-enantioselective reduction of model biaryl hydroxy aldehydes,[29] but had not yet been applied to natural product synthesis. The stereoselective reduction of **15** (Scheme 4) gave similar atropisomeric ratios as in the previous lactone reduction (*cf.* Scheme 2), confirming the assumption[30] that both reactions go through similar intermediates and are governed by the same principles of stereocontrol.

The preparation of no less than three naphthylisoquinoline alkaloids 'at one blow', by efficient regioselective intramolecular coupling of the ester-type prefixed molecular moieties and atropo-divergent ring-cleavage or, optionally, by the first application of an atropo-divergent biaryl hydroxy aldehyde reduction, underlines the efficiency of our lactone coupling methodology for the preparation of biologically active biaryl alkaloids. Further applications of the method are under investigation.



diastereomeric ratios of **12**

'H⁻'	M:P
$LiAlH_4$	53:47
$AlMe_3/LiAlH_4$	60:40
$NaBH_4$	55:45
Red-Al	35:65
L-Selectride	79:21
(*S*)-**16**·BH_3	>95:5
(*R*)-**16**·BH_3	18:82

Scheme 4. Atropodiastereo-divergent reduction of the hydroxy aldehyde / lactol mixture **15**.

EXPERIMENTAL

Melting points were measured on a Reichert-Jung Thermovar hot-plate and are uncorrected. IR spectra were taken on a Perkin-Elmer 1420 infrared spectrophotometer, and reported in wave numbers (cm^{-1}). NMR spectra were recorded with a Bruker AC 200, a Bruker WM 400, a Bruker AC 250, and a Bruker DMX 600 spectrometer. The chemicals shifts δ are given in parts per million (ppm) with the proton signals in the deuterated solvent as internal reference for ^1H and ^{13}C NMR. The coupling constants, *J*, are given in Hertz. HPLC analyses, hexane / isopropanol (93:7; 1 ml/min) as the eluent, were carried out with a combination of a Waters HPLC pump 510, a 20 µl injection loop and a Chiralcel OD column (0.46 x 25 cm) with UV detection at 280 nm. The retention times are: *P*-**12** 19 min and *M*-**12** 24 min. Mass spectra were obtained on a Finnigan MAT 8200 and a Finnigan MAT 90 mass spectrometer at 70 eV in the EI mode unless otherwise stated. Elemental analyses were performed by the Microanalytical Laboratory of the University of Würzburg on a LECO CHNS-932 instrument. TLC: precoated silica gel 60 F_{254} plates (Merck).

(1*R*,3*R*)-(*N*-Benzyl-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-8-*O*-yl) 1'-Bromo-5'-isopropoxy-4'-methoxy-2'-naphthoate (9). To a suspension of 200 mg (0.59 mmol) **7**[7] in 25 ml dry CH_2Cl_2 and one drop of dry DMF, 60 µl (0.68 µmol) of oxalyl chloride were added dropwise under N_2 atmosphere at 0 °C. After 5 min, the reaction mixture was allowed to warm to room temperature, and then added slowly to a solution of 200 mg (0.57 mmol) of **8**[21], 1.2 g NEt_3 in 5 ml dry CH_2Cl_2, and a catalytic amount of DMAP over a period of 30 min. After removal of the solvent *in vacuo*, the residue was recrystallized from methanol to give **9** (294 mg, 85%) as colorless crystals; mp 120 °C; $[\alpha]_D^{20}$ = +7.2 (*c* = 0.35 in methanol); IR (KBr): $\tilde{\nu}$ 2960, 2920 (C-H), 1750 (C=O), 1580, 1560 (C=C), 1210 (C-O); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.7 Hz, 3H, 1-CH_3 or 3-CH_3), 1.35 (d, *J* = 6.0 Hz, 3H, 3-CH_3 or 1-CH_3), 1.38 (d, *J* = 6.0 Hz, 6H, $C(CH_3)_2$), 2.70 (d, *J* = 7.5 Hz, 2H, 4-H), 3.26 (d, *J* = 13.6 Hz, 1H, CH_2-Ph), 3.58 (m_C, 1H, 3-H), 3.71 (s, 3H, 4'-OCH_3), 3.88 (d, *J* = 13.6 Hz, 1H, CH_2-Ph), 4.03 (q, *J* = 6.9 Hz, 1H, 1-H), 6.79 (s, 1H, 3'-H), 7.03-8.06 (m, 12H, Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.6, 20.8, 21.9, 31.3, 45.6, 49.5, 51.3, 56.1, 73.4, 104.9, 113.2, 114.8, 120.0, 121.9, 126.5, 126.8, 128.1, 128.3, 128.9, 130.9, 131.2, 135.4, 136.9, 140.5, 148.6, 155.2, 156.8, 165.6; MS: *m/z* (%) = 575 (33) [M^++ H], 574/572 (100) [M^+]; Anal. calcd. for $C_{33}H_{34}BrNO_4$ (588.5): C, 67.54; H, 5.90; N, 2.48. Found:

C, 67.34; H, 5.82; N, 2.37.

***N*-Benzyl-5'-*O*-isopropyldioncolactone A (10).** A mixture of **9** (150 mg, 0.25 mmol), NaOAc (75.0 mg, 0.75 mmol), and $PdCl_2(PPh_3)_2$ (53.0 mg, 0.075 mmol) in 40 ml of dry *N,N*-dimethylacetamide (DMA) was heated to 130 °C. The solvent was removed under reduced pressure, 5 ml of CH_2Cl_2 were added, and the mixture was filtered over Celite. Removal of the solvent *in vacuo* afforded **10** (116 mg, 92%) as an amorphous yellow powder; $[\alpha]_D^{20}$ = +17.8 (*c* = 0.25 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 2960, 2920 (C-H), 1715 (C=O), 1580 (C=C), 1115 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.6 Hz, 3H, 1-CH_3 or 3-CH_3), 1.45 (d, *J* = 6.0 Hz, 6H, $C(CH_3)_2$),1.57 (d, *J* = 6.7 Hz, 3H, 3-CH_3 or 1-CH_3), 2.76 (d, *J* = 7.7 Hz, 2H, 4-H), 3.35 (d, *J* = 14.3 Hz, 1H, C*H*$_2$-Ph), 3.63 (m_c, 1H, 3-H), 3.82 (d, *J* = 14.3 Hz, 1H, C*H*$_2$-Ph), 4.06 (s, 3H, 4'-OCH_3), 4.41 (q, *J* = 6.8 Hz, 1H, 1-H), 4.61 (m_c, 1H, *H*C$(CH_3)_2$), 7.06-7.70 (m, 10H, Ar-H), 8.15 (d, *J* = 8.1 Hz, 1H, 6-H or 8'-H), 8.42 (d, *J* = 8.5 Hz, 1H, 8'-H or 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.2, 20.3, 21.1, 21.6, 31.6, 45.5, 49.7, 51.6, 55.9, 73.3, 101.6, 115.5-140.2, 148.2, 155.2, 157.2, 170.5; MS: *m/z* (%) = 507 (1) [M^+], 493 (7) [M^+ + H - CH_3], 492 (20) [M^+ - CH_3]; Anal. calcd. for $C_{33}H_{33}NO_4$ (507.5): C, 78.60; H, 6.57; N, 2.68. Found: C, 78.08; H, 6.55; N, 2.76.

***N*-Benzyldioncolactone A (11).** To a solution of 40.0 mg (0.08 mmol) **10** in 20 ml dry CH_2Cl_2, BCl_3 (0.20 ml, 0.20 mmol, 1M in CH_2Cl_2) was added at -50 °C. After 15 min, 2 ml MeOH were added and the solvent was removed under reduced pressure. Column chromatography with CH_2Cl_2 / methanol (100:2) as the eluent and subsequent recrystallization from *tert*-butyl methyl ether / methanol afforded **11** (34 mg, 92%) as yellow needles; mp 217 °C; $[\alpha]_D^{20}$ = +33.8 (*c* = 0.05 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3380 (OH), 2950, 2920 (C-H), 1710 (C=O), 1590 (C=C), 1110, 1100 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ =1.25 (d, *J* = 6.6 Hz, 3H, 1-CH_3 or 3-CH_3), 1.48 (d, *J* = 6.7 Hz, 3H, 3-CH_3 or 1-CH_3), 2.69 (d, *J* = 7.7 Hz, 2H, 4-H), 3.26 (d, *J* = 14.3 Hz, 1H, C*H*$_2$-Ph), 3.55 (m_c, 1H, 3-H), 3.86 (d, *J* = 14.3 Hz, 1H, C*H*$_2$-Ph), 4.09 (s, 3H, 4'-OCH_3), 4.30 (q, *J* = 6.7 Hz, 1H, 1-H), 6.99-7.52 (m, 9H, Ar-H), 8.09 (d, *J* = 8.4 Hz, 1H, 6-H or 8'-H), 8.23 (d, *J* = 8.5 Hz, 1H, 8'-H or 6-H), 9.46 (s, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.5, 20.7, 32.3, 45.9, 50.3, 52.0, 57.0, 101.3, 114.9, 116.6, 119.2, 124.7, 124.8, 126.9, 128.5, 129.2, 132.0, 155.6, 156.5; MS: *m/z* (%) = 466 (1) [M^+ + H], 465 (2) [M^+], 451 (32) [M^+ + H - CH_3], 450 (100) [M^+ - CH_3]; Anal. calcd. for $C_{30}H_{27}NO_4$ (465.5): C, 77.23; H, 5.83; N, 2.82. Found: C, 77.40; H, 5.84; N, 3.01.

Dioncolactone A (4). Lactone **11** (50.0 mg, 0.11 mmol) was hydrogenated in methanol (5 ml) in the presence of Pd/C (10%) (10.0 mg) for 10 h under normal hydrogen pressure. After filtration of the catalyst through Celite, the solvent was removed and the residue was crystallized from methanol, yielding **4** (36.0 mg, 86%) as yellow needles; mp 82 °C; $[\alpha]_D^{20}$ = -64.0 (*c* = 0.26 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3380 (OH), 2940, 2910, 2840 (C-H), 1710 (C=O), 1590 (C=C), 1110 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.3 Hz, 3H, 3-CH_3 or 1-CH_3), 1.54 (d, *J* = 6.7 Hz, 3H, 1-CH_3 or 3-CH_3), 2.48 (dd, J_{gem} = 16.9 Hz, J_{ax} = 10.9 Hz, 1H, 4-H_{ax}), 2.83 (dd, J_{gem} = 17.0 Hz, J_{eq} = 3.9 Hz, 1H, 4-H_{eq}), 3.33 (m_c, 1H, 3-H), 4.11 (s, 3H, 4'-OCH_3), 4.69 (q, *J* = 6.7 Hz, 1H, 1-H), 6.97-7.08 (m, 2H, Ar-H), 7.43-7.51 (m, 2H, Ar-H), 8.07 (d, *J* = 8.4 Hz, 1H, 6-H or 8'-H), 8.19 (d, *J* = 8.5 Hz, 1H, 8'-H or 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.9, 22.7, 37.3, 41.7, 47.4, 56.8, 101.0, 114.8, 116.1, 118.2, 119.0, 119.7, 124.7, 124.9, 129.1, 129.8, 131.6, 136.9, 147.4, 155.4, 156.2, 161.3; MS: *m/z* (%) = 376 (7) [M^+ + H], 375 (20) [M^+], 374 (38) [M^+ - H], 361 (27) [M^+ + H – CH_3], 360 (100) [M^+ - CH_3]. The compound was found to be fully identical with an authentic sample of dioncolactone A previously obtained from *T. peltatum*.[13]

***N*-Benzyldioncopeltine A (*M*-12) and *N*-Benzyl-7-*epi*-dioncopeltine A (*P*-12).** To a solution of 50.0 mg (0.10 mmol) of **11** in 3 ml dry THF, $LiAlH_4$ (82.0 mg, 2.28 mmol) was added under N_2 atmosphere at

-60 °C, and stirred for 30 min. Removal of the solvent and chromatography of the residue on silica gel with CH_2Cl_2 / methanol (90:10) as the eluent afforded the diastereomers ***M*-12** and ***P*-12** (56:44) as amorphous powders; ***M*-12**: 22.1 mg (47%); $[\alpha]_D^{20}$ = +49.1 (*c* = 0.78 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3380 (OH), 2950, 2920 (C-H), 1590 (C=C), 1225, 1180, 1115 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18-1.33 (m, 6H, 1-CH_3 and 3-CH_3), 2.67 (d, *J* = 6.9 Hz, 2H, 4-H), 3.37 (d, *J* = 14.1 Hz, 1H, C*H*$_2$-Ph), 3.52 (m$_C$, 1H, 3-H), 3.84 (d, *J* = 14.0 Hz, 1H, C*H*$_2$-Ph), 3.97 (q, *J* = 6.6 Hz, 1H, 1-H), 4.06 (s, 3H, 4'-OCH_3), 4.41 (s, 2H, C*H*$_2$OH), 6.71-7.33 (m, 10H, Ar-H), 9.36 (s, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.2, 19.4, 29.6, 32.4, 45.8, 50.3, 51.7, 56.2, 63.4, 104.0, 111.1, 114.8, 117.2, 121.2, 121.3, 124.7, 126.6, 126.9, 128.2, 128.3, 128.6, 136.3, 136.5, 138.5, 141.0, 150.9, 154.9, 156.9; MS: *m/z* (%) = 469 (1) [M$^+$], 455 (32) [M$^+$ + H – CH_3], 454 (100) [M$^+$ - CH_3]; Exact mass calcd. for $C_{30}H_{31}NO_4$ (M$^+$) 469.2253. Found: 469.2251. ***P*-12**: 22 mg (47%); $[\alpha]_D^{20}$ +8.5 (*c* = 0.42 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3380 (OH), 2950, 2920 (C-H), 1560 (C=C), 1225, 1180, 1115 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16-1.33 (m, 6H, 1-CH_3 and 3-CH_3), 2.67 (d, *J* = 7.7 Hz, 2H, 4-H), 3.36 (d, *J* = 14.2 Hz, 1H, C*H*$_2$-Ph), 3.40 (m$_C$, 1H, 3-H), 3.84 (d, *J* = 14.3 Hz, 1H, C*H*$_2$-Ph), 3.97 (q, *J* = 6.8 Hz, 1H, 1-H), 4.04 (s, 3H, 4'-OCH_3), 4.43 (s, 2H, C*H*$_2$OH), 6.74-7.34 (m, 10H, Ar-H), 9.33 (s, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.2, 19.4, 29.6, 32.4, 45.8, 50.3, 51.7, 56.2, 63.4, 104.0, 111.1, 114.8, 117.2, 121.2, 121.3, 124.7, 126.6, 126.9, 128.2, 128.3, 128.6, 136.3, 136.5, 138.5, 141.0, 150.9, 154.9, 156.9; MS: *m/z* (%) = 469 (1) [M$^+$], 455 (31) [M$^+$ + H – CH_3], 454 (100) [M$^+$ - CH_3], 437 (20) [M$^+$ + H – CH_3 - H_2O], 436 (61) [M$^+$ - CH_3 - H_2O]; Exact mass calcd. for $C_{30}H_{31}NO_4$ (M$^+$) 469.2253. Found: 468.2251.

Dioncopeltine A (5). In analogy to the synthesis of **4**, ***M*-12** (20.0 mg, 0.04 mmol) was hydrogenated in to give **5** (12.0 mg, 80%) as colorless needles; mp 233 °C (ref.[13] 233-234 °C); $[\alpha]_D^{20}$ = -13.0 (*c* = 0.53 in $CHCl_3$) [ref.[13] -13.1 (*c* = 0.53 in $CHCl_3$)]; IR (KBr): $\tilde{\nu}$ 3500 (OH), 3320, 3280 (NH), 2940, 2910, 2840 (C-H), 1600 (C=C), 1380 (CH_3), 1235, 1110 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.3 Hz, 3H, 3-CH_3), 1.45 (d, *J* = 6.7 Hz, 3H, 1-CH_3), 2.53 (dd, J_{gem} = 16.5 Hz, J_{ax} = 10.7 Hz, 1H, 4-H_{ax}), 2.83 (dd, J_{gem} = 16.7 Hz, J_{eq} = 4.0 Hz, 1H, 4-H_{eq}), 3.36 (m$_C$, 1H, 3-H), 4.15 (s, 3H, 4'-O CH_3), 4.40 (q, *J* = 6.7 Hz, 1H, 1-H), 4.50 (s, 2H, C*H*$_2$OH), 6.76-6.90 (m, 3H, Ar-H), 7.09 (s, 1H, 3'-H), 7,21-7.31 (m, 2H, Ar-H), 9.41 (s, 1H, 5'-OH); ^{13}C NMR (62 MHz, pyridine-d$_5$): δ = 21.6, 23.2, 38.4, 42.4, 48.6, 55.9, 62.4, 104.0, 110.2, 114.9, 117.7, 120.7, 122.6, 126.8, 127.9, 129.3, 129.9, 136.3, 137.5, 140.6, 152.7, 155.5, 156.3; MS: *m/z* (%) = 379 (11) [M$^+$], 364 (100) [M$^+$ - CH_3]. The compound was found to be fully identical with an authentic sample of dioncopeltine A previously obtained from *T. peltatum*.[13]

N*-Benzyl-8-*O*-benzyldioncopeltine A (13)**. A solution of 200 mg (0.40 mmol) of *N*-benzyldioncopeltine A (M*-12**) in 10 ml dry acetone was treated with 302 mg (0.91 mmol) of Cs_2CO_3 and 100 µl (0.84 mmol) of benzyl bromide. After stirring under reflux for 8 h, Cs_2CO_3 was filtered off and the solvent was removed *in vacuo*. Column chromatography (CH_2Cl_2) and subsequent recrystallization from CH_2Cl_2 / petroleum ether afforded *N-b*enzyl-8-*O*-benzyldioncopeltine A (**13**) (183.0 mg, 96%) as colorless crystals; mp 150 °C (ref.[14] 150° C); $[\alpha]_D^{20}$ = +61.8 (*c* = 0.53 in $CHCl_3$) [ref.[14] +61.8 (*c* = 0.53 in $CHCl_3$)]; IR (KBr): $\tilde{\nu}$ 3370 (OH), 3060, 3035, 3005, 2950, 2900 (C-H), 1590 (C=C), 1222, 1109, 1068 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25-1.31 (m, 6H, 1-CH_3 and 3-CH_3), 2.72 (d, *J* = 7.9 Hz, 2H, 4-H), 3.48 (d, *J* = 13.7 Hz, 1H, C*H*$_2$-Ph), 3.51 (m$_C$, 1H, 3-H), 3.78 (d, *J* = 9.7 Hz, 1H, C*H*$_2$-Ph), 3.84 (d, *J* = 9.7 Hz, 1H, C*H*$_2$-Ph), 3.87 (d, *J* = 13.7 Hz, 1H, C*H*$_2$-Ph), 3.97 (q, *J* = 6.3 Hz, 1H, 1-H), 4.08 (s, 3H, 4'-OCH_3), 4.22 (s, 2H, C*H*$_2$OH), 6.16-6.25 (m, 2H, 5-H and 6-H), 6.81-7.38 (m, 16H, Ar-H), 9.44 (s, 1H, 5'-OH); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 19.3, 19.9, 33.1, 45.6, 50.6, 51.8, 56.4, 71.1, 73.8, 106.9, 108.5, 116.3, 119.4, 119.9, 126.2, 126.9, 127.2, 127.5, 127.6, 128.0, 128.3, 128.6, 133.4, 134.6, 135.9, 136.9, 137.7, 140.6, 155.1, 156.3, 156.9; MS: *m/z* (%) = 560 (1) [M$^+$ + H], 559 (3) [M$^+$], 545 (36) [M$^+$ + H – CH_3], 544 (89) [M$^+$ - CH_3], 91 (100) [$C_7H_7^+$]. The compound was found to be

fully identical with an authentic sample prepared previously by partial synthesis.[14]

***N*-Benzyl-8-*O*-benzyl-5'-*O*-demethyldioncophylline A (14).** To a solution of **13** (78.0 mg, 0.14 mmol) in dry CH_2Cl_2 (6 ml), PPh_3 (74.0 mg, 0.28 mmol) and $(BrCl_2C)_2$[26] (92.0 mg, 0.28 mmol) were added under N_2 atmosphere. After stirring for 10 min at room temperature, the solvent was evaporated and the residue was dissolved in 6 ml dry THF. Then, 123.0 mg (3.42 mmol) $LiAlH_4$ were added at -78 °C. After stirring for 5 min at 0 °C, 5 ml of 2 N HCl were cautiously added. The solvent was evapd and the residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (CH_2Cl_2) afforded **14** (66.0 mg, 87%) as an amorphous yellow powder; $[\alpha]_D^{20}$ = +28.8 (*c* = 0.51 in $CHCl_3$) [ref.[14] +28.8 (*c* = 0.51 in $CHCl_3$)]; IR (KBr): $\tilde{\nu}$ 3375 (OH), 3060, 3035, 3005, 2945, 2910 (C-H), 1593 (C=C), 1250, 1220, 1110 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 3.2 Hz, 3H, 1-CH_3 or 3-CH_3), 1.36 (d, *J* = 3.0 Hz, 3H, 3-CH_3 or 1-CH_3), 2.15 (s, 3H, 2'-CH_3), 2.75-2.79 (m, 2H, 4-H), 3.51 (d, *J* = 13.7 Hz, 1H, C*H*$_2$-Ph), 3.60 (m_C, 1H, 3-H), 3.88-4.04 (m, 3H, 1-H and C*H*$_2$-Ph), 4.09 (s, 3H, 4'-OCH_3), 6.41 (d, *J* = 8.1 Hz, 1H, 5-H or 6-H), 6.42 (d, *J* = 7.8 Hz, 1H, 6-H or 5-H), 6.70-7.44 (m, 16H, Ar-H), 9.43 (s, 1H, 5'-OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.7, 20.3, 21.1, 33.9, 45.7, 50.7, 51.9, 56.8, 71.6, 107.4, 108.5, 116.9, 119.8, 120.1, 126.8, 126.8, 127.5, 127.9, 127.6, 127.9, 128.0, 128.3, 128.4, 128.6, 133.5, 134.7, 135.6, 136.2, 136.9, 137.4, 140.6, 154.8, 156.1; MS: *m/z* (%): 544 (1) [M^+ + H], 543 (2) [M^+], 529 (40) [M^+ + H – CH_3], 528 (100) [M^+ - CH_3], 91 (42) [$C_7H_7^+$]. The compound was fully identical with an authentic sample prepared previously by partial synthesis.[14]

5'-*O*-Demethyldioncophylline A (6). In analogy to the synthesis of **4**, compound **14** (15.0 mg, 27.6 μmol) was hydrogenated to give **6** (6.6 mg, 66%); mp 233 °C (ref.[14] 233 °C); $[\alpha]_D^{20}$ = -11.3 (*c* = 0.015 in $CHCl_3$) [ref.[14] -11.3 (*c* = 0.015 in $CHCl_3$)]; IR (KBr): $\tilde{\nu}$ 3400 (OH), 2950, 2910 (C-H), 1610, 1590 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.1 Hz, 3H, 3-CH_3), 1.37 (d, *J* = 6.1 Hz, 3H, 1-CH_3), 2.09 (s, 3H, 2'-CH_3), 2.45 (dd, J_{gem} = 16.5 Hz, J_{ax} = 11.0 Hz, 1H, 4-H_{ax}), 2.72 (dd, J_{gem} = 16.5 Hz, J_{eq} = 3.8 Hz, 1H, 4-H_{eq}), 3.27 (m_C, 1H, 3-H), 4.00 (s, 3H, 4'-OCH_3), 4.32 (q, *J* = 6.5 Hz, 1H, 1-H), 6.65 (s, 1H, 3'-H), 6.66 (d, *J* = 7.1 Hz, 1H, 8'-H), 6.73-6.76 (m, 3H, 6'-H, 5-H and 6-H), 7.12 (dd, *J* = 8.1 Hz, *J* = 7.9 Hz, 1H, 7'H), 9.24 (s, 1H, 5'-OH); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 20.6, 20.9, 22.6, 37.3, 41.8, 47.5, 53.3, 56.0, 76.6, 76.9, 77.1, 106.6, 110.2, 113.7, 116.7, 120.9, 122.0, 124.7, 128.3, 128.3, 135.4, 136.1 136.3, 149.4, 154.6, 156.1; MS: *m/z* (%): 364 (7) [M^+ + H], 363 (19) [M^+], 349 (29) [M^+ + H – CH_3], 348 (100) [M^+ - CH_3], 333 (15) [M^+ - 2 CH_3]. The compound was found to be fully identical with an authentic sample of 5'-*O*-demethyldioncophylline A isolated from *T. peltatum*.[14]

Oxidation of *M*-12, *P*-12, or Diastereomeric Mixtures thereof, to the Hydroxy Aldehyde / Lactol 15a/15b Mixture. 2.5 equivalents of pyridinium chlorochromate (PCC) were added in portions at 0 °C to a solution of 20 mg (0.04 mmol) of the alcohol *M*/*P*-**12** in THF. After stirring at room temperature for 2 h, the reaction mixture was quenched with water, extracted with diethyl ether, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (petroleum ether / diethyl ether 10:1 → 4:1) to yield 14.5 mg (73%) of the hydroxy aldehyde / lactol mixture **15a/15b** as an amorphous powder; MS: *m/z* (%): 467 (3) [M^+], 452 (42) [M^+ – CH_3], 91 (100) [$C_7H_7^+$]; Exact mass calcd. for $C_{29}H_{26}NO_4$ [M^+ - CH_3]: 452.1860. Found: 452.1862.

***N*-Benzyldioncolactone A (11).** To a solution of **15a/15b** (30.0 mg, 64.2 μmol) in dioxan (2 ml), glacial acetic acid (1 ml, 15.9 mmol) and the solutions of NaOAc (26.0 mg, 1.92 mmol) in H_2O (1 ml), sulphamic acid (12.5 mg, 128.4 μmol) in H_2O (1 ml) and NaO_2Cl (11.9 mg, 128.4 μmol) in H_2O (1 ml) were added consecutively. After stirring for 4 h at room temperature, the solvent was removed under reduced pressure. The

residue was dissolved in CH_2Cl_2 (25 ml), washed with H_2O (3 × 10 ml) and dried (K_2CO_3). Evaporation of the solvent and recrystallization of the crude product from Et_2O / petroleum ether afforded **11** (19.5 mg, 65%) as yellow needles; mp 217 °C; $[\alpha]_D^{20}$ = +33.8 (*c* = 0.05 in $CHCl_3$); For further data, see above.

General Procedure for the Oxazaborolidine-Assisted Borane-Reduction of the Lactone 11 and the Hydroxy Aldehyde / Lactol Mixture 15a/15b, Respectively (Analytical Scale). To a solution of 4 equivalents of BH_3·THF (1.0 M solution in THF), a solution of 3 equivalents of oxazaborolidine *S*-**16** or *R*-**16** (1.0 M solution in THF) was added at 0 °C under an argon atmosphere. The reaction mixture was warmed to 30 °C, then a solution of 1 equivalent of lactone **11** or hydroxy aldehyde / lactol mixture **15a/15b** in THF was added dropwise during 10 min, and stirring was continued for 2 h. The reaction mixture was quenched with 2 N HCl and extracted with diethyl ether. The organic solution was purified by TLC with CH_2Cl_2 / methanol (100:3) as the eluent and then examined by HPLC.

General Procedure for the Reduction of 11 and 15a/15b, Respectively, with $AlMe_3$-$LiAlH_4$ (Analytical Scale). To a solution of 1 equivalent of **11** or the **15a/15b** mixture in THF, 2 equivalents of $AlMe_3$ were added at 0 °C. After 2 min, the mixture was cooled to -40 °C, then a solution of 2 equivalents of $LiAlH_4$ was added, and stirring was continued for 2 h, then the mixture was allowed to warm up to room temperature. Work up as described above.

General Procedure for the Reduction of 11 and 15a/15b, Respectively, with other Reducing Agents (Analytical Scale). To a solution of 1 equivalent of **11** or the **15a/15b** mixture in THF, the reducing agent (2 equivalents $NaBH_4$, 2.5 equivalents Red-Al, or L-Selectride) was added at 0 °C (for $NaBH_4$) or -78 °C (for Red-Al and L-Selectride), and stirring was continued for 2 h. Work up as described above.

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