ing stages, any diastereoisomer contamination of **6a** or **6b** would be apparent from an examination of the camphanate methyl resonances in the $^1$H NMR spectra. At no stage was any such contamination seen. A two-step deprotection strategy involving removal of the benzyl protecting groups on phosphates by hydrogenolysis and then cleavage of camphanate esters in a concentrated solution of ammonia at 60 °C was effective with no migration of phosphate groups.[11] Tetrakis(phosphate)s **2a** and **2b** could then be isolated on a gram scale as the cyclohexylammonium[7a] or potassium[7d] salts in overall yields of 60–70% from **4a** and **4b**. The structures of **2a** and **2b** were confirmed by $^1$H, $^{13}$C, and $^{31}$P NMR spectroscopy as well as high-resolution FAB-MS. We recently used bulk material prepared in this fashion to investigate the submolecular acid–base properties of Ins(1,3,4,5)$P_4$ by $^{31}$P NMR titration experiments.[12] Alternatively, ion-exchange chromatography on Q-Sepharose Fast-Flow gave the pure tetrakisphosphates as their triethylammonium salts. A sample of **2a** was identical to biologically-derived D-Ins(1,3,4,5)$P_4$ with respect to its interaction with GAP1$^{IP4BP}$.

In conclusion, we describe rapid access to pure synthetic D- and L-Ins(1,3,4,5)$P_4$ from readily available starting materials by simultaneously using camphanate esters as desymmetrizing auxiliaries and protecting groups. This strategy should have wider applicability in the inositol phosphate field. Furthermore, the technique is capable of providing D-Ins(1,3,4,5)$P_4$ in quantities that will now be required for crystallographic and NMR studies of its interaction with the rapidly expanding range of Ins(1,3,4,5)$P_4$-binding proteins.

*Experimental Section*

**4a, b**: To a stirred suspension of **3** (2.00 g, 10.5 mmol) in dry $CH_2Cl_2$ (40 mL) at 0 °C were added $Et_3N$ (3.3 mL, 23.7 mmol) and a catalytic amount of 4-dimethylaminopyridine (80 mg). A solution of (1*S*)-(−)-camphanic acid chloride (4.55 g, 21.0 mmol) in dry $CH_2Cl_2$ (10 mL) was added dropwise under an $N_2$ atmosphere at 0 °C. The cooling bath was removed after 30 min, and stirring continued for a further 30 min. After this time almost no solid remained, and TLC ($CH_2Cl_2$/ethyl acetate 3/1) showed two major products at $R_f = 0.32$ and 0.23. The solvents were removed in vacuo, and the residue was purified by flash chromatography ($CH_2Cl_2$/ethyl acetate 4/1) to give first **4a** (3.46 g, 6.28 mmol, 60% yield) and then **4b** (1.35 g, 2.45 mmol, 23% yield).

**2a, b**: A solution of **6a** or **6b** in MeOH/$H_2O$ (19/1) was stirred vigorously with 10% Pd/C under an atmosphere of $H_2$ at room temperature overnight. The catalyst was removed by filtration, and the solvents in vacuo. The residue was dissolved in a concentrated solution of aq ammonia, and the solution stirred at 60 °C in a sealed Pyrex autoclavable bottle for 6 h. The solution was allowed to cool and then concentrated under reduced pressure. The residue was dissolved in deionized water, and the camphanamide removed by washing with $CH_2Cl_2$ (3 ×) followed by $Et_2O$. Purification by ion-exchange chromatography on Q-Sepharose Fast-Flow eluting with a gradient of triethylammonium bicarbonate buffer (pH 8, 0–1 M) gave the pure triethylammonium salts of **2a** or **2b**, which eluted at 730–850 mM buffer. For larger-scale production treatment with Dowex 50 $H^+$ resin gave solutions of the free acids of **2a** or **2b**, which were washed again with $CH_2Cl_2$ and $Et_2O$, and then converted into either the cyclohexylammonium [7a] or potassium [7d] salts in quantitative yield from **6a** or **6b**.

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[10] Crystal structure analysis of **4a**: Suitable crystals were grown by slow crystallization from 2-propanol (approximate crystal dimensions 0.3 × 0.3 × 0.3 mm): $C_{27}H_{34}O_{12}$, $M_r = 550.54$, monoclinic, $a = 6.755(1)$, $b = 31.139(2)$, $c = 7.035(1)$ Å, $\beta = 117.80(1)^\circ$, $V = 1309.0(3)$ Å$^3$, space group $P2_1$, $Z = 2$, $\rho_{calcd} = 1.397$ g cm$^{-3}$, $\mu(Mo_{K\alpha}) = 0.110$ mm$^{-1}$, $F(000) = 584$. Measurements were made at 293(2) K on a CAD4 automatic four-circle diffractometer in the range $2.61 < \theta < 21.93^\circ$. Data (1795 reflections) were corrected for Lorentzian and polarization but not for absorption effects. In the final least-squares cycles all atoms were allowed to vibrate anisotropically. Except for H1A, which was located in the penultimate difference Fourier and refined at a distance of 0.96 Å from O4, hydrogen atoms were included at calculated positions where relevant. The supramolecular structure contains a hydrogen-bonding feature. The structure was solved with SHELX86 and refined with SHELX93: based on 1326 with $F_o > 4\sigma(F_o)$ $R1 = 0.0318$ and $wR2 = 0.0755$; GOF = 1.029; max./min. residual densities 0.185/ − 0.175 e Å$^{-3}$. The asymmetric unit (Figure 1) and the labeling scheme were produced with ORTEX. Final fractional atomic coordinates, anisotropic temperature factors, and bond distances and angles are available as supplementary data. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100275. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223)336-033; e-mail: deposit@chemcrys.cam.ac.uk).

[11] An earlier strategy involving phosphitylation with bis(cyanoethyloxy)-*N*,*N*-diisopropylaminophosphine/1*H*-tetrazole and oxidation as before followed by a one-step deprotection with aqueous ammonia was not satisfactory. It gave rise to slight but detectable migration of phosphate groups at the deprotection stage.

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# A New Cationic Domino Process to (±)-Uleine

Monika H. Schmitt and Siegfried Blechert*

*Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 65th birthday*

Domino processes play an important role in organic synthesis,[1] and cation-induced processes are of great significance in both organic synthesis and biosynthesis. Herein we report on a new cationic cascade reaction (Scheme 1), which we have applied to the stereoselective synthesis of uleine. The introduced process might also be very interesting for the construction of strychnos alkaloids.

Several syntheses have been described for the alkaloids of the uleine group such as uleine (**2**), which like the strychnos alkaloids has an azocino[4,3-*b*]indole skeleton.[2] However, most concepts that employ a carbocyclization in a late step (either by formation of the C-1/C-9a or C-4/C-4a bond) lead to 3-*epi*-com-

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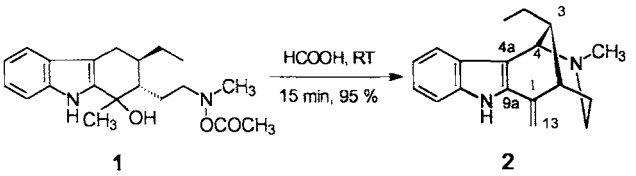
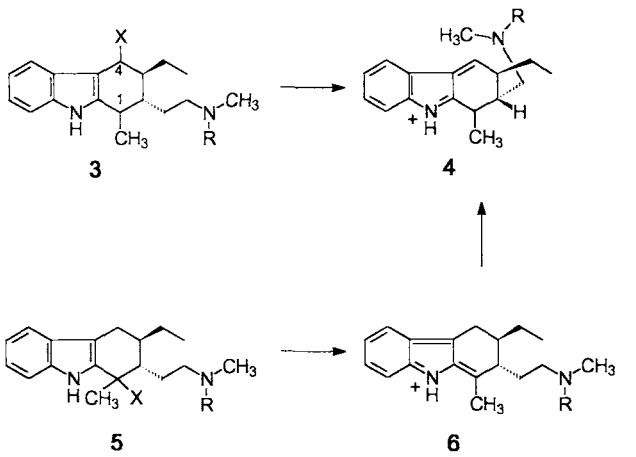



1 2

Scheme 1. Cation-induced transformations of **1** to uleine (**2**).

pounds. Therefore, for the synthesis of uleine (**2**) we envisaged a heterocyclization from the side opposite the ethyl group to form the piperidine ring. Ring closure should occur via an iminium ion of type **4** (Scheme 2) and should lead to the desired configuration at C-3. Cations of type **4** should be readily available by cleaving a suitable leaving group X from **3**, as described

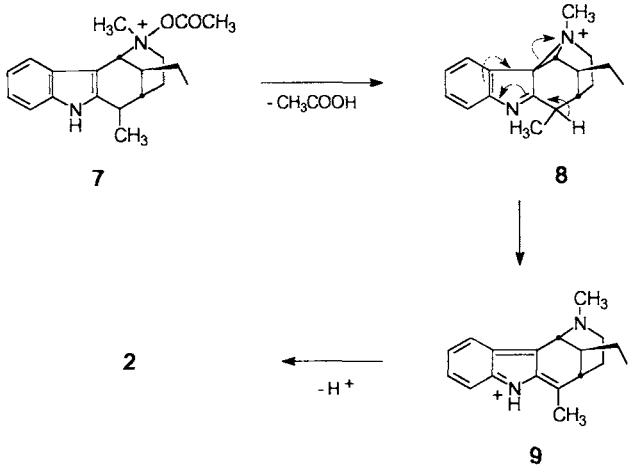


3 4 5 6

Scheme 2. Proposed routes to the vinylic iminium salt **4**.

in syntheses of similar systems.[3] We assumed that this iminium ion could also be formed by a leaving group on C-1 (uleine nomenclature). The cation **6** generated from **5** could undergo isomerization to the thermodynamically favored product **4** by a deprotonation–protonation sequence faster than addition of a nucleophile. In our concept, a positive charge generated on C-1 would activate position C-4 for nucleophilic attack. To the best of our knowledge a reaction like this has not yet been described in indole chemistry. However, the heterocyclization would give a 1,13-dihydrouleine. To construct the double bond, we planned a new cation-induced process. The *N*-acyloxyammonium ion **7** resulting from the heterocyclization step should be a suitable precursor for this reaction (Scheme 3). Because of the short distance between C-4a and the nitrogen atom of the piperidine ring and the convenient orientation of the $\pi$ electrons to this nitrogen, an intramolecular substitution reaction could lead to **8**, containing a three-membered ring and an imine group. Tautomerization of **8** to **9** and subsequent removal of a proton to the vinylindole, would lead to uleine (**2**). Whereas, during the first reaction step, a carbocation on the "southern part of the molecule" should lead to a reaction in the "northern part", a cationic nitrogen center in the "northern area" should form the C-1/C-13 double bond. Generation of the ammonium ion **7** by the above-mentioned cyclization reaction serves to connect both processes.

This concept, which may seem speculative at first glance, proved viable. Thus, the *O*-acylated hydroxylamine derivative **1**, which was used as a mixture of two diastereomeres with regard to the configuration at C-1, was allowed to react with formic acid at room temperature to give uleine (**2**) in high yield (Scheme 1). The spectroscopic data of **2** are in agreement those




7 8 2 9

Scheme 3. Proposed mechanism for the formation of the C-1/C-13 double bond in **2** from the *N*-acyloxyammonium ion **7**.

of the natural product.[4] The structure was confirmed by comparison with an authentic sample. On the basis of our findings we propose the mechanism given in Schemes 2 and 3 for the synthesis of uleine; however, as of yet we have no definite proof. We tried to monitor the reaction by NMR spectroscopy, but we could not detect any clearly definable intermediates. Instead of tertiary alcohol **1**, the *exo*-methylene compound resulting from the removal of $H_2O$ can be employed. We have prepared 1,13-dihydrouleine-$N_b$-oxide form **2** by hydrogenation with palladium and barium sulfate and subsequent conversion with *m*-chloroperbenzoic acid; its reaction with acetyl chloride at low temperature was then monitored by NMR spectroscopy. Salt **7**-Cl was formed at $-40\,^{\circ}C$ and transformed into uleine at $-30\,^{\circ}C$. Unfortunately, intermediates could not be confirmed. Several attempts at gaining indications of radical processes also proved unsuccessful. The transformation **7** → **2** is much faster than the overall process. The formation of the aziridinium ion could not be verified, but seems reasonable to us on the basis of results obtained form experiments with the *N*-acylated cationic uleine-*N*-oxide. Ions of type **7** with a double bond between C-1 and C-13 give products of a nucleophilic addition to C-13.

The devised domino process consists of the following steps: formation of a benzyl cation, multistep tautomerizations, cyclization to the piperidine derivative, formation of a three-membered ring, fragmentation, and tautomerization.

The synthesis of **1** is described in Scheme 4; each compound was fully characterized. Starting from cyclohexenone **10**, Michael addition followed by conversion of the enolate by alkylation,[5] and treatment with sodium hydride and ethylformiate yield the *trans*-configurated hydroxymethylene compound **11** in good yield.[6] A Japp–Klingemann reaction and subsequent Fischer indole synthesis give rise to the tetrahydrocarbazole **12**.[7] Unfortunately, the *trans* configuration is partially affected during the course of the Fischer indole synthesis. A complete isomerization to **12** is achieved by treatment with sodium methanolate in methanol after a reaction time of 1–2 weeks at room temperature. Evidently, the competing deprotonation of the acidic NH proton and the slight CH acidity of the vinylogous amide delay the isomerization to the thermodynamically favored *trans* product **12**. The subsequent oxidative cleavage of the double bond with a catalytic amount of osmium tetroxide and sodium periodate leads to the aldehyde, which reacts without further purification with *N*-methylhydroxylamine to give hydroxylamine **13** under reductive conditions (sodium cyanoborohydride) at pH 6. The formation of the tetrahydro-

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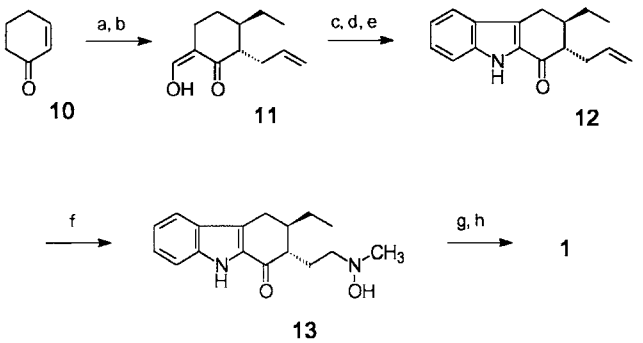


Scheme 4. a) 1. EtMgBr, CuI, $Me_2S$, THF; 2. $H_2C{=}CHCH_2Br$, hexamethylphosphoric acid triamide (HMPT) (60%); b) NaH, glyme, HCOOEt (95%); c) $PhN_2Cl$ (85%); d) HCOOH (86%); e) NaOMe, MeOH, RT, 12–14 d (99%); f) 1. $OsO_4$, $NaIO_4$, MTBE, $H_2O$; 2. MeNHOH, $NaCNBH_3$, *i*PrOH, pH = 6 (85%); g) MeLi, THF, $-20\,^{\circ}C \rightarrow$ RT (98%); h) $Ac_2O$, pyridine, 3 h, RT (99%).

carbazole derivative **1** is achieved by the addition of methyllithium to the carbonyl function, and O-acetylization of the hydroxylamine group.[9] The conversion of **13** to uleine (**2**) can be performed in good yields without chromatographic purification of the intermediates. The novel cascade reaction allows the application of the readily obtained *trans* configuration of the tetrahydrocarbazole **13** for a concise and stereoselective synthesis of uleine. This example demonstrates once more that the application of domino processes can open more efficient and shorter synthetic pathways.

### *Experimental Section*

**2**: Tetrahydrocarbazole **1** (68.8 mg, 0.2 mmol) was dissolved in formic acid (5 mL) and left at room temperature for 15 min. The solvent was evaporated under reduced pressure and the crude product was purified by preparative thin-layer chromatography (silical gel, $CH_2Cl_2$/MeOH, 95/5 under $NH_3$ atmosphere) to give (±)-uleine (**2**) (54 mg, 95%).

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[9] Selected spectroscopic data of **1**: $^1$H NMR (400 MHz, $CDCl_3$, TMS): $\delta$ = 7.44 (dd, $J$ = 8 Hz, $J$ = 1 Hz, 1H, H-5), 7.29 (dd, $J$ = 8, 1 Hz, 1H, H-8), 7.13 (ddd, $J$ = 8, 8, 1 Hz, 1H, H-7), 7.07 (ddd, $J$ = 8, 8, 1 Hz, 1H, H-6), 3.15 (m, 1H, H-13), 2.99 (dd, $J$ = 16.5, 5 Hz, 1H, H-4), 2.85 (m, 1H, H-13'), 2.77 (s, 3H, H-14), 2.22 (dd, $J$ = 16.5, 10 Hz, 1H, H-4'), 2.05 (s, 3H, H-17), 1.76 (m, 4H, H-2, H-3, H-12, H-12'), 1.40 (s, 3H, H-15), 1.28 (m, 2H, H-10, H-10'), 0.98 (t, $J$ = 7 Hz, 3H, H-11).

# Relative Migratory Aptitude of Substituents and Stereochemistry of Dyotropic Ring Enlargements of β-Lactones

Johann Mulzer,* Karsten Hoyer, and Anke Müller-Fahrnow

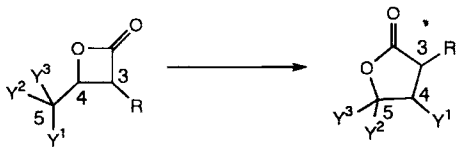
*Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday*

In a dyotropic reaction of type 1 two substituents change their positions relative to a C–C single bond (Scheme 1).[1] The mutual 1,2 shift is reversible if there is no significant energy


Scheme 1.

difference between the two tautomers. In the case of a concerted mechanism the shift follows a *syn* or *anti* stereochemistry. The latter is characterized by an inversion at C1 and C2. If, on the other hand, the 1,2 shift proceeds by a stepwise mechanism, there is no compulsory correlation between the configurations of the two centers. Apart from the stereochemistry the migratory aptitude of the substituents is a point of issue about which practically nothing is known so far.

We report here on the dyotropic ring enlargement of β-lactones to γ-lactones. These rearrangements are irreversible due to ring-strain relief (Scheme 2) and proceed by inversion at C4.[2]




Scheme 2.

The relative migratory aptitude can be determined by placing different substituents $Y^1$, $Y^2$, and $Y^3$ at C5 of the β-lactone. We examined substituents with σ- (Y = alkyl), π- (Y = phenyl), and *n*- (Y = OR) donor qualities. In the last case the reaction resembles a semipinacol rearrangement.[3] The stereochemistry of the rearrangement with respect to the C4–C5 axis was studied with C3 as a stereochemical reference. The reaction can proceed by the concerted mechanism **A** or the stepwise-ionic mechanism **B** (Scheme 3).[2, 4, 5]

If mechanism **A** is involved the reaction should exclusively form γ-lactone **2** by a twofold inversion at C4 and C5. Conversely, in mechanism B a cationic species **Z-1** is generated, which may form **Z-2** by rotation about the C4–C5 axis. Intermediates **Z-1** and **Z-2** can cyclize to the epimeric γ-lactones **2** and **3**, respectively.[2] The experimental data are summarized in Table 1.

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