On the Conformations of Halichlorine and the Pinnaic Acids: Nitrogen Inversion as a Possible Determinant of Biological Profile

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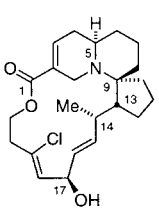
Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

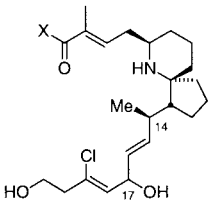
Although the marine alkaloids halichlorine (**1**) and the pinnaic acids **2**, which contain a quinolizidine ring system, exhibit considerable structural homology, they act upon different biological targets (VCAM-1 and $cPLA_2$, respectively). Quinolizidines can exist as *cisoid* or *transoid* invertomers. In the recently reported total synthesis of (+)-halichlorine, it was determined by NMR that advanced intermediates **3** and **4**, containing the spiroquinolizidine core, exhibit the *transoid* conformation, while the macrolactone-containing halichlorine has the *cisoid* conformation. We conclude that constraints imposed upon closure of the macrolactone ring force adoption of the *cisoid* conformation. The major conformational reorganization upon macrolactonization has implications for the design of pharmacophors and anticipated structure-activity relationships in their action on biological targets.

Halichlorine (**1**) [1] and the pinnaic acids (**2a**, **2b**) [2], marine alkaloids recently isolated by *Uemura* and co-workers, exhibit considerable structural homology. Halichlorine was found to selectively inhibit the induced expression of VCAM-1 (Vascular Cell Adhesion Molecule-1) [3]. By contrast, pinnaic acid and tauropinnaic acid were identified in an assay aimed at the identification of specific inhibitors of cytosolic phospholipase A_2 ($cPLA_2$). Since both VCAM-1 and $cPLA_2$ play key roles in the inflammatory cascade, such agents might be useful in the discovery and development of novel drugs against various diseases, including autoimmunity disorders and cancer. The value of such compounds as leads could be much enhanced through a clearer understanding of their solution conformations. In the course of our recent total synthesis of (+)-halichlorine [4], we came upon several interesting findings in this regard. We noticed that crucial NMR-spectral features of a series of advanced intermediates incorporating the spiroquinolizidine framework (**3a**–**3e**, **4a**–**4b**) bore little resemblance to those of halichlorine itself. In particular, the chemical shifts and the coupling patterns observed for the bridgehead H-atoms at C(5) (*e.g.*, for compound **3a**: $\delta = 2.37$ ppm, *dddd*, $J = 3.6, 3.8, 10.5, 11.3$ Hz) clearly differ from the corresponding ones found in halichlorine ($\delta = 3.18$ ppm, *dddd*, $J = 1.5, 2.0, 6.5, 13.0$ Hz) [1]. Since extensive NMR studies and an X-ray crystal structure of a subsequent derivative (*vide infra*) allowed us to unambiguously assign the configuration of our intermediate spiroquinolizidines **3**–**4**, a rationale for these strikingly different spectroscopic features was sought.

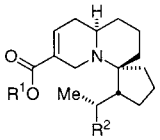
Quinolizidines can exist as *cisoid* or *transoid* invertomers [5]. We propose that halichlorine adopts a *cisoid* conformation (see **5**). This perception is at some variance



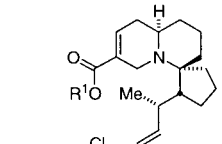
1 halichlorine



2a X = OH, pinnaic acid
2b X = $NH(CH_2)_2SO_3$, tauropinnaic acid

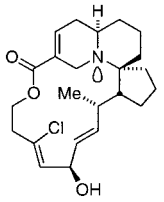


3a R^1 = *t*-Bu, R^2 = CH_2OH
3b R^1 = *t*-Bu, R^2 = CHO
3c R^1 = H, R^2 = $CH_2OTBDPS$
3d R^1 = *t*-Bu, R^2 = C≡CH
3e R^1 = *t*-Bu, R^2 = $CH=CH_2$
3f R^1 = *t*-Bu, R^2 = CH=CHI

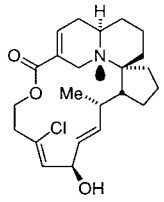


4a R^1 = *t*-Bu, R^2 = TBS, R^3 = H
4b R^1 = H, R^2 = H, R^3 = TBS
4c R^1 = Me, R^2 = H, R^3 = H

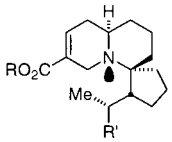
with *Uemura*'s argument (based on an apparent *Bohlmann* band), which concluded that halichlorine displays a *transoid*-quinolizidine ring system (**6**) [1]. Molecular-modeling studies performed with *Macromodel*™ (version 6.5; MM2 force-field) [6] suggest **5** to be the lowest energy conformer (*Fig. 1*). Moreover, the ^{1}H-NMR coupling patterns observed for halichlorine can be readily rationalized from the *cisoid* conformer **5** shown in *Fig. 1*. Furthermore, the NOESY cross-peaks – in particular those between H–C(10b) and the $C(21)H_3$ group – can be nicely accommodated *via* **5**. By contrast, in a *transoid* conformer such as **6**, the proximity of these protons would not be close enough to give rise to NOE enhancements.



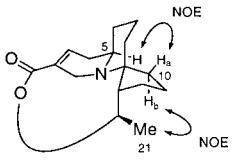
5 *cisoid*

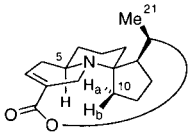


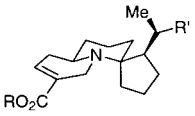
6 *transoid*



3a–**4c** *transoid*







Interestingly, the synthetic precursors **3a**–**3e** and **4a**, **4b** all adopt *transoid* conformations as evidenced by the chemical shifts and the coupling patterns of the H-atoms at C(5) (two large and two small coupling constants). *Apparently, the constraints imposed by the 15-membered macrolactone ring force the quinolizidine ring of halichlorine into a* cisoid *conformation*. In the absence of this constraint, the heterocyclic ring system relaxes into the *transoid* form, which is normally found to be lower in energy in the quinolizidine series [5]. This is particularly conspicuous, both in seco-acid **4b** or its methanolysis product **4c**.

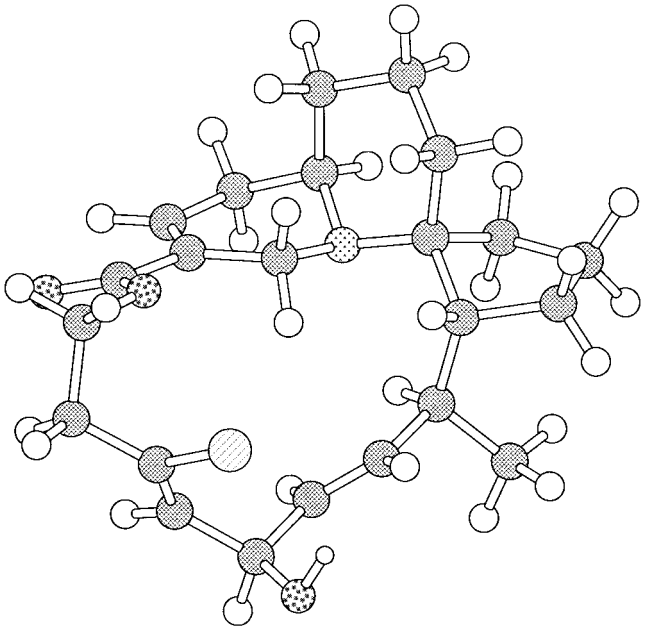
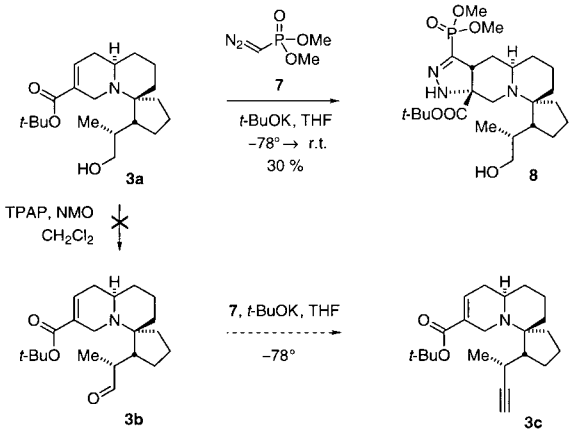


Fig. 1. *Calculated lowest-energy conformer of halichlorine.* The calculations were performed with *Macromodel V.6.5* (5000-step *Monte-Carlo* simulation, MM2 force-field).

The relative configuration of our advanced synthetic intermediates **3a**–**3f** was unambiguously proven by an X-ray crystallographic analysis of a 'serendipitously' obtained derivative, compound **8** (*Scheme 1*). Attempted oxidation of amino alcohol **3a** to the corresponding amino aldehyde **3b** using tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) [7] proved to be highly capricious. Due to its instability, **3b** was immediately subjected to the next step, an attempted alkynylation with *Gilbert*'s reagent (dimethyl diazophosphonate, **7**) [8], without benefit of full purification. Furthermore, the tertiary amines **3a** and **3b** could not be distinguished by standard TLC analysis. In one instance, the oxidation failed, leaving a large percentage of unreacted starting material **3a** in the crude reaction mixture. Not surprisingly, in retrospect, the ensuing treatment with **7** and *t*-BuOK afforded none of the desired alkyne **3c** but instead resulted in the formation of the interesting phosphono derivative **8**. This compound proved to be a crystalline material (m.p. 178° (dec.)), enabling the determination of its three-dimensional structure by X-ray crystallography. In a formal sense, this reaction can be seen as a 1,3-dipolar cycloaddition, followed by tautomerization. Alternatively, the mechanism commences with conjugate addition of the corresponding anion of **7** to the unsaturated ester moiety. This is followed in a separate step by intermolecular addition of the ester enolate to the diazo group and subsequent protonation. The high facial stereoselectivity of this reaction is remarkable. Indeed, compound **8** was formed as the only detectable diastereoisomer.

As shown in *Fig. 2*, the quinolizidine ring system of phosphono compound **8** resides in a *transoid* conformation wherein the lone-pair of the N-atom and the bridgehead H-

Scheme 1



atom at C(5) point in opposite directions (*Fig. 2*). The NMR data of **8** (500 MHz, CD_3OD) are in accordance with this observation and suggest that a similar conformation is adopted in solution. The corresponding *cisoid* conformation is

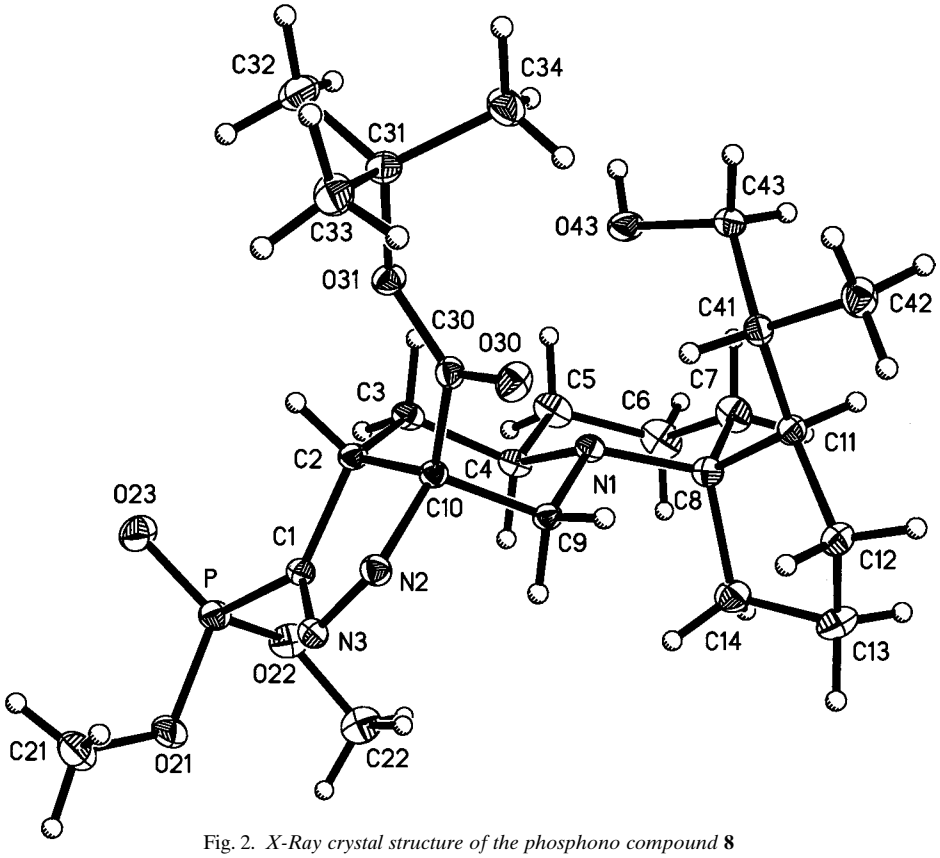
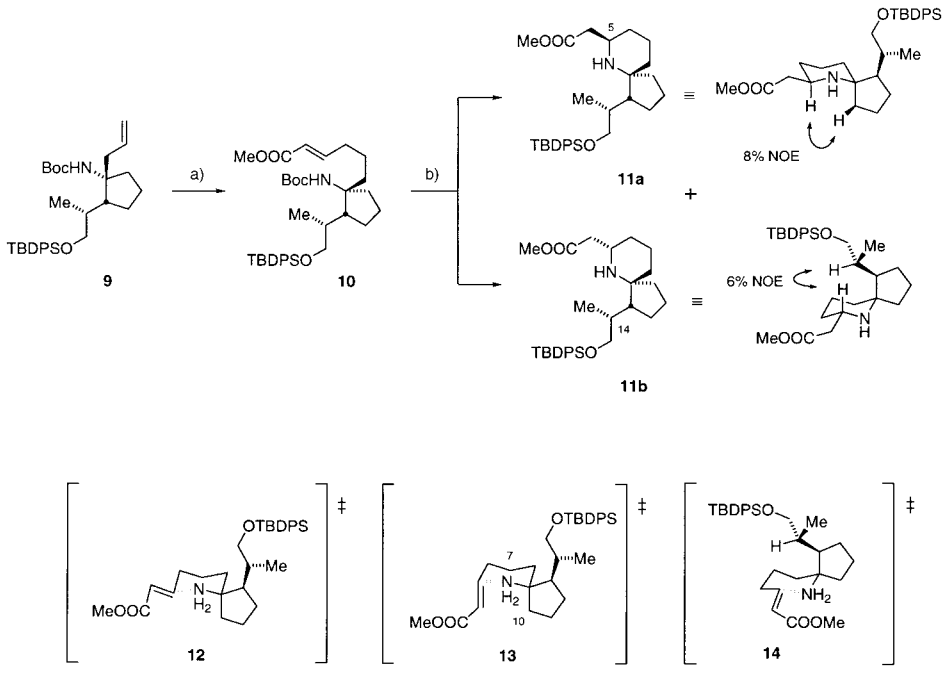


Fig. 2. *X-Ray crystal structure of the phosphono compound* **8**

probably further disfavored by severe interactions between the *t*-BuOCO group and the spirocyclopentane ring.

Another interesting conformational 'switch' involving the aza-spirobicyclic core of halichlorine and the pinnaic acids was observed during the earlier stages of our synthesis. In one of the key transformations of this effort, the azaspiro[4.5]decane system was stereoselectively formed through a novel *Suzuki-Michael* reaction sequence. Hydroboration of alkene **9** followed by Pd^0-mediated cross-coupling with methyl (*E*)-3-iodoacrylate afforded the unsaturated ester **10** (*Scheme 2*). Subsequent removal of the Boc protecting group triggered a rapid intramolecular *Michael* addition to afford piperidine **11a**/**11b** as a 20:1 mixture of diastereoisomers. The comparatively high rate of this cyclization could well reflect a prominent *Thorpe-Ingold* effect [9]. Furthermore, the gratifying stereochemical outcome of this cyclization can be explained in terms of a chair-shaped transition state **12**, wherein all the larger substituents adopt *pseudo*-equatorial positions. Clearly, unfavorable 1,3-diaxial interactions are less pronounced in transition state **12** than in transition states **13** and **14**, the latter two giving rise to the minor diastereoisomer **11b**. A fourth conceivable chair-shaped transition state leading to **11a**, wherein both the α,β-unsaturated ester moiety and the more highly substituted cyclopentane-carbon reside in *pseudo*-axial positions, can be ruled out for all practical purposes. In full accordance with these transition-state models, an analogous sequence performed with the corresponding (*Z*)-iodoacrylate led

Scheme 2



a) 1. 9-Borabicyclo[3.3.1]nonane (9-BBN), THF; 2. (*E*)-I-CH=CH−COOMe, 10% [$PdCl_2$(dppf)], $AsPh_3$, Cs_2CO_3, DMF, H_2O. b) 1. CF_3COOH, CH_2Cl_2; 2. H_2O, K_2CO_3 (67% overall yield from **9**; **11a**/**11b** 20:1).

to the exclusive formation of **11a** in good overall yield [4]. In this case, the destabilizing 1,3-diaxial interactions discussed above can be expected to be even more pronounced.

Interestingly, the overall conformation adopted by the piperidine ring of the azaspiro[4.5]decane core depends on the relative configuration at C(5) (*Scheme 2*). The conformations of **11a** and **11b** were elucidated by detailed analysis of their ^{1}H-NMR spectra. In structure **11a**, the more substituted C-atom of the cyclopentane is equatorial to the piperidine ring. Permutation of the stereocenter C(5) as shown in epimeric intermediate **11b** brings with it ring inversion of the piperidine ring [10]. Attempts to actually interconvert **11a** and **11b** *via* a *retro-Michael* reaction proved unsuccessful in our hands. The pinnaic acids themselves have been suggested to adopt a conformation similar to that of **11a** [2]. It remains to be clarified whether inversion of the conformation at C(14) (*i.e.*, upon passing from the halichlorine to the presumed pinnaic acid series [2]) is also influential in dictating the overall conformation of the aza-spirobicyclic core[1]).

The finding that macrolactonization and inversion of the stereocenter C(5) brings with it a major conformational reorganization has considerable implications in the design of pharmacophors and in anticipating likely structure-activity relationship patterns (SARs) of halichlorine and the pinnaic acids. As mentioned above, both agents contact apparently completely different targets (VCAM-1 and $cPLA_2$, resp.), although the overall biological consequences are similar. This behavior could well result from differences in the shape of the azabicylic moieties of the molecules. Given our recently gained capability of reaching halichlorine by total synthesis, and given the fact that relatively early intermediates such as **11a** seem to embody the conformation of the pinnaic acids, the elements required for an SAR analysis that is sensitive to changes in configuration are in place. Such studies should establish the extent to which conformational inversion controls the dominance of halichlorine *vs.* pinnaic acid character in determining the biological profile of the various congeners.

Experimental Part

tert-*Butyl 1′-(Dimethoxyphosphonyl)-3′a,4′,7′,8′,9′,9′a,10′,10′a-octahydro-2-(2-hydroxy-1-methylethyl)spiro-[cyclopentane-1,6′(6′*H*)-[3*H*]pyrazolo[4,3-b]quinolizine]-3a-carboxylate* (**8**). To a soln. of **3a** (349 mg, 1 mmol) in MeCN (25 ml) was added *N*-methylmorpholine-*N*-oxide (NMO; 234 mg, 2 mmol) followed by powdered 4-Å molecular sieves (1 g) and tetrapropylammonium perruthenate (TPAP; 35 mg, 0.1 mmol). After stirring for 2 h at r.t., the mixture was concentrated *in vacuo* and filtered over a short column of silica gel, eluting with AcOEt. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in THF (20 ml), cooled to $-78°$, and treated with dimethyl diazophosphonate (7 ml of a 0.57M soln. in THF, 4 mmol) and *t*-BuOK (4 ml of a 1M soln. in THF, 4 mmol). The yellow mixture was stirred at $-78°$ for 12 h and then warmed to r.t. within 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (10 ml), and the mixture was extracted with Et_2O (4×50 ml). The combined org. phases were dried (Na_2SO_4) and concentrated *in vacuo*, to afford a partially crystalline residue. Silica-gel chromatography (hexanes/AcOEt 1:1) afforded pure **8** (150 mg, 0.3 mmol; 30%). Colorless needles. Part of the material was recrystallized from CH_2Cl_2/pentane. $C_{24}H_{42}N_3O_6P$, M_r 499.58 g · mol^{-1}. M.p.: 178° (dec.). $[\alpha]_D^{20} = +16.8$ ($c = 1.08$, $CHCl_3$). IR ($CHCl_3$): 3213, 2952, 2870, 2820, 1735, 1448, 1369, 1256, 1165, 1035, 836, 749. ^{1}H-NMR (500 MHz, CD_3OD): 0.89 (*d*, $J = 6.6$, 3 H); 1.21 (*m*, 1 H); 1.40–1.61 (*m*, 18 H); 1.74 (*m*, 1 H); 1.97–2.21 (*m*, 6 H); 2.32 (*m*, 1 H); 3.20 (*d*, $J = 12,1$ H); 3.40–3.47 (*m*, 3 H); 3.78 (*d*, $J = 11$, 3 H); 3.80 (*d*, $J = 11$, 3 H). ^{13}C-NMR (125 MHz, CD_3OD): 19.44; 23.01; 25.31; 28.58; 29.98; 31.73; 33.91; 35.61; 37.78; 42.24; 47.84; 48.02;

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[1]) Similar observations were made by *Lee* and *Zhao* in the course of their own approach towards halichlorine and pinnaic acid [10].

52.48; 54.43 ($d, J = 6$); 54.70 ($d, J = 6$); 56.50; 62.37; 69.72; 70.50; 73.31 ($d, J = 6$); 84.48; 145.63 ($d, J = 229$); 170.30. ESI-MS: 437.8, 494.1 ($[M + H]^+$).

X-Ray Crystal Structure of **8**. X-Ray crystal data for $C_{24}H_{42}N_3O_6P$: monoclinic, space group $P2_1$, $D_c = 1.259\ g \cdot cm^{-3}$, $Z = 2$, $a = 6.8950(6)$ Å, $b = 19.4123(18)$ Å, $c = 9.9041(9)$ Å, $\beta = 97.117(2)^\circ$, $V = 1315.4(2)$ Å^3, MoK_α radiation, $\lambda = 0.71073$ Å, $2.07 \leq \Theta \leq 28.12$, 5277 unique reflections, $T = 313(2)$ K. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-square analysis (SHELXL-97). Final $R(F) = 0.0319$, $wR/(F^2) = 0.0888$ for 314 parameters and 5277 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for compound **8** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC 144411. Copies of the data can be obtained, free of charge, from: The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

*Methyl (1S,2R)-6-(1-[(*tert*-Butoxy)carbonylamino]-2-[(1R)-2-[(*tert*-butyl)diphenylsilyloxy]-1-methylethyl}cyclopentyl)hex-2-enoate* (**10**), *Methyl (1R,5S,7R)-(1-[(1R)-2-[(*tert*-butyl)diphenyl silyloxy]-1-methylethyl}-6-azaspiro[4.5]dec-7-yl)acetate* (**11a**) *and (1R,5S,7S)-(1-[(1R)-2-[(*tert*-butyl)diphenylsilanoxy]-1-methylethyl}-6-azaspiro[4.5]dec-7-yl)acetate* (**11b**). A soln. of 9-BBN in THF (0.5M, 10 ml, 5 mmol) was added dropwise to a soln. of **9** (1.57 g, 3 mmol) in THF (25 ml). The borane soln. was stirred at r.t. for 1.5 h and then transferred to a vigorously stirred mixture of (*E*)-I-CH=CH–COOMe (1.27 g, 6 mmol), $[PdCl_2(dppf) \cdot CH_2Cl_2$ (245 mg, 0.3 mmol), Ph_3As (92 mg, 0.3 mmol), Cs_2CO_3 (1.63 g, 5 mmol), H_2O (0.72 ml, 40 mmol) in DMF (10 ml) *via* double-tipped needle. After stirring for 3 h, the dark red mixture was poured into H_2O (50 ml) and extracted with Et_2O (5×20 ml). The org. phase was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was partially purified by chromatography on a short silica-gel column (hexanes/AcOEt 10:1) to afford the crude enoate **10**, along with other unidentified compounds of similar polarity, as a colorless oil. An anal. sample of **10** was obtained by further chromatographic purification (hexanes/AcOEt 10:1). The remaining crude material (2.01 g) was dissolved in CH_2Cl_2 (30 ml) and treated with CF_3COOH (10 ml). After stirring at r.t. for 1 h, the mixture was poured into H_2O (50 ml). The aq. phase was basified by careful addition of solid K_2CO_3 and was then thoroughly extracted with CH_2Cl_2 (5×20 ml). The combined org. phases were dried ($MgSO_4$) and evaporated. The residue was purified by silica-gel chromatography (hexanes/AcOEt $40:1 \rightarrow 20:1 \rightarrow 10:1$) to afford **11a** (978 mg, 1.93 mmol, 64%) as a colorless oil. Further elution with AcOEt gave **11b** (50 mg, 0.098 mmol, 3%) as a colorless oil.

Data of **10**: Colorless oil. $C_{36}H_{53}NO_5Si$, M_r 607.90 $g \cdot mol^{-1}$. $[\alpha]_D^{20} = +5.7$ ($c = 0.52$, $CHCl_3$). IR (film): 2953, 2858, 1724, 1505, 1269, 1244, 1169, 1112, 1085. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.86 ($d, J = 7.1$, 3 H); 1.04 (s, 9 H); 1.35–1.72 (m, 8 H); 1.40 (s, 9 H); 1.79 (m, 1 H); 2.00–2.19 (m, 5 H); 3.39–3.46 (m, 2 H); 3.70 (s, 3 H); 4.51 (br. s, 1 H); 5.78 ($d, J = 15.9$, 1 H); 6.92 ($dt, J = 7.1$, 1 H); 7.34–7.43 (m, 6 H); 7.63–7.66 (m, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.67; 17.52; 19.97; 21.61; 24.26; 25.17; 26.72; 30.88; 32.76; 35.44; 36.42; 47.62; 49.59; 63.08; 67.28; 119.22; 125.89; 127.87; 132.04; 133.91; 147.70; 153.32; 165.35. ESI-MS: 630.4 ($[M + Na]^+$).

Data of **11a**: Colorless oil. $C_{31}H_{45}NO_3Si$, M_r 507.79 $g \cdot mol^{-1}$. $[\alpha]_D^{20} = -24.6$ ($c = 1.00$, $CHCl_3$). IR (film): 2930, 2857, 1735, 1471, 1428, 1111, 702. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (m, 1 H); 0.93 ($d, J = 6.6$, 3 H); 1.05 (s, 9 H); 1.13 (m, 1 H); 1.34–1.64 (m, 11 H); 1.79 (m, 1 H); 1.92 (m, 1 H); 2.21 ($dd, J = 8.2, 15.5$, 1 H); 2.32 ($dd, J = 4.4, 15.5$, 1 H); 3.00 (m, 1 H); 3.50 ($dd, J = 6.9, 9.5$, 1 H); 3.65–3.68 (m, 1 H); 3.65 (s, 3 H); 7.35–7.42 (m, 6 H); 7.65–7.68 (m, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.62; 19.32; 22.38; 22.53; 26.83; 26.96; 32.55; 34.47; 35.80; 35.99; 41.88; 48.40; 50.85; 51.38; 63.16; 68.94; 127.52; 129.42; 134.25; 135.69; 173.19. ESI-MS: 508.4 ($[M + H]^+$).

Data of **11b**: Colorless oil. $C_{31}H_{45}NO_3Si$, M_r 507.79 $g \cdot mol^{-1}$. $[\alpha]_D^{20} = +17.6$ ($c = 1.32$, $CHCl_3$). IR (film): 2930, 2857, 1738, 1472, 1428, 1171, 1111, 1084, 833, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.81 ($d, J = 7.5$, 3 H); 1.04 (s, 9 H); 1.09–1.24 (m, 2 H); 1.49–1.64 (m, 10 H); 2.07 (br. s, 1 H); 2.14 (m, 1 H); 2.29–2.44 (m, 3 H); 3.04 (m, 1 H); 3.37–3.47 (m, 2 H); 3.64 (s, 3 H); 7.33–7.41 (m, 6 H); 7.64–7.66 (m, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.28; 20.92; 21.79; 22.90; 24.84; 28.54; 33.72; 34.01; 38.22; 34.92; 40.99; 43.66; 51.07; 53.12; 66.11; 70.26; 129.25; 131.19; 135.69; 137.31; 174.38. ESI-MS: 508.3 ($[M + H]^+$), 530.3 ($[M + Na]^+$).

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