reaction with 5.3 equivalents of Bu_4NBrCl_2 at $-55\,^{\circ}C$ under an argon atmosphere gave halomon (**1**: 25%; 42% based on recovery of **8**) and the diastereomer (**9**: 8%) together with recovered **8** (40%). The racemic halomon ((±)-**1**) was separated by reversed-phase HPLC (Cosmosil 5PYE; CH_3CN/water 60/40); its ^1H and ^{13}C NMR spectra[2a] are identical with those of natural halomon.[12] Furthermore, pure natural enantiomer (+)-**1** was isolated by HPLC using DAICEL CHIRALPAK AD-RH (CH_3CN/water 54/46) as colorless needles (from EtOH): m.p. 56.0–57.2 °C; $[\alpha]_D^{25} = +42.6$ ($c = 1.0$, CH_2Cl_2); ref.[2a] m.p. 49–50 °C; $[\alpha]_D$ +206 ($c = 1.08$, CH_2Cl_2). The structure of synthetic (+)-**1** was unambiguously confirmed by X-ray crystallographic analysis. Optically pure synthetic (−)-**1**, which was also isolated, exhibited $[\alpha]_D^{25} = -40.2$ ($c = 0.75$, CH_2Cl_2). Therefore, the reported large value of $[\alpha]_D$ for natural halomon[2a] appears to arise from some impurity.

Thus, we have achieved the total synthesis of halomon (**1**) in only three steps from myrcene. This synthesis indicates the possible biosynthesis pathway of **1**.[1] Further research directed towards a stereocontrolled and enantioselective total synthesis of halomon and its congeners is currently under way in our laboratory.

Experimental Section

5, **6**, **7**: Bu_4NBrCl_2 (0.94 g, 2.4 mmol) was added to a solution of **3** (0.17 mL, 1.0 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with diethyl ether (10 mL), washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to chromatography on silica gel (hexane) to yield an approximate 1:2 mixture of **5** and **6** (0.23 g, 0.63 mmol, 63%) together with **7** (34 mg, 0.090 mmol, 8%).

8: DBU (75 μL, 0.50 mmol) was added to a solution of a 0.6:1 mixture of **5** and **6** (0.59 g, 1.6 mmol) in DMF (15 mL), and the mixture was stirred at room temperature for 1.2 h. The reaction mixture was poured into a vigorously stirred mixture of ice–water (30 mL) and hexane (30 mL). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (SiO_2, hexane) of the products gave **8** (0.11 g, 0.39 mmol, 78% from **5**) and the recovered **6** (0.36 g, 97% recovery).

1: Bu_4NBrCl_2 (14 g, 36 mmol) was added to a solution of **8** (1.95 g, 6.8 mmol) in CH_2Cl_2 (60 mL) under an argon atmosphere at $-55\,^{\circ}C$, and the solution was allowed to stir at $-55\,^{\circ}C$ for five days. 2-Methyl-2-butene (7.8 mL, 74 mmol) was added to the reaction mixture at $-55\,^{\circ}C$ until the yellow color faded. The reaction mixture was diluted with hexane (60 mL), washed with water and brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The product was purified by flash column chromatography (SiO_2, hexane) to yield a 3:1 mixture of **1** and **9** (0.93 g, 2.3 mmol, 33%) and the recovered **8** (0.79 g, 2.8 mmol, 40%). Compound **1** was separated from **9** by HPLC (Cosmosil 5PYE; CH_3CN/water 60/40); **9** eluted as a shoulder on the front-side of the peak of **1**. HPLC of (±)-**1** using DAICEL CHIRALPAK AD-RH (CH_3CN/water 54/46) gave the enantiomers; (−)-**1** was eluted prior to natural (+)-**1**.

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[1] B. J. Burreson, F. X. Wollard, R. E. Moore, *Chem. Lett.* **1975**, 1111.

[2] a) R. W. Fuller, J. H. Cardellina II, Y. Kato, L. S. Brinen, J. Clardy, K. M. Snader, M. R. Boyd, *J. Med. Chem.* **1992**, *35*, 3007; b) R. W. Fuller, J. H. Cardellina II, J. Jurek, P. J. Scheuer, B. Alvarado-Lindner, M. McGuire, G. N. Gray, J. R. Steiner, J. Clardy, E. Menez, R. H. Shoemaker, D. J. Newman, K. M. Snader, M. R. Boyd, *J. Med. Chem.* **1994**, *37*, 4407.

[3] For synthetic studies of the congeners and related compounds, see: a) M. E. Jung, M. H. Parker, *J. Org. Chem.* **1997**, *62*, 7094; b) A. L. Boyes, M. Wild, *Tetrahedron Lett.* **1998**, *39*, 6725.

[4] For the first synthesis of **1**, see:T. Schlama, R. Baati, V. Gouverneur, A. Valleix, J. R. Falck, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2226; *Angew. Chem. Int. Ed.* **1998**, *37*, 2085.

[5] a) T. Negoro, Y. Ikeda, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2111; b) T. Negoro, Y. Ikeda, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2547.

[6] The ratio was determined by HPLC analysis (Cosmosil 5C18-MS 4.6 × 150 mm, MeOH/H_2O 80/20, 1 mL min^{-1}).

[7] Acetonitrile was also usable, while the reaction became too sluggish in hexane, and side reactions occurred in DMF.

[8] Neither the positions of the added bromine and chlorine atoms nor the geometry of the double bond were determined.

[9] The presence of four diastereomers was revealed by NMR spectroscopy.

[10] Separation of **5** and **6** by HPLC was inconvenient. Therefore, the mixture of **5** and **6** was treated with DBU without separation to yield the diene **8** and the recovered **6**, which were easily separated by flash chromatography (see Experimental Section).

[11] N. Ichikawa, Y. Naya, S. Enomoto, *Chem. Lett.* **1974**, 1333.

[12] We are grateful to Dr. Michael R. Boyd and Prof. C. Mioskowski for providing a ^1H NMR spectrum of (+)-**1** and ^1H NMR data for racemic **1** and **9**.

Synthesis of a Triazatriangulenium Salt

Bo W. Laursen* and Frederik C. Krebs

Stabilized carbenium ions such as the triarylmethyl, xanthyl, and acridinium cations are organic compounds of great scientific and commercial importance. Many of them are used as textile and laser dyes, as well as in various fluorescent probes and cellular stains for biological and diagnostic purposes.[1–3] Consequently, their thermodynamic and photophysical properties have been extensively studied, and great effort has been put into clarifying the relationship between structure and stability[4, 5] as well as into synthesizing new carbenium ions with very high stability.[6, 7] Aromatic nucleophilic substitution (S_NAr) with amines on *para*-methoxy- or *para*-chloro-substituted carbenium ions has proven a powerful tool in the preparation of a variety of new triaryl carbenium ions.[8–10] Until now no substitution of *ortho* groups in these ions has been described. Herein we report the synthesis of a novel and extremely stable trimethyl triaza-

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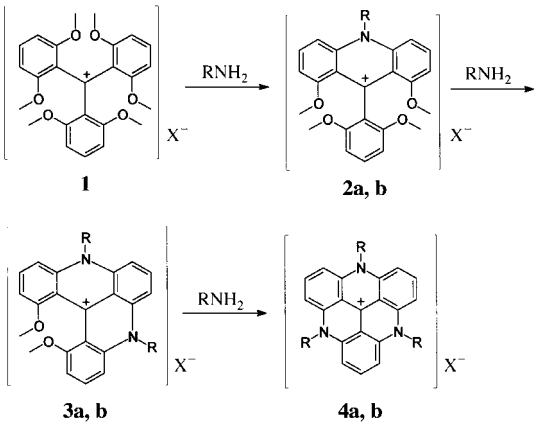
triangulenium salt formed from the known carbenium salt **1** (see Scheme 1) through three consecutive *ortho* S_NAr reactions in a one-pot procedure.

The tetrafluoroborate salt of carbenium ion **1** was obtained in excellent yield (97%) from the corresponding carbinol,[11] by treatment with HBF_4. This carbenium ion has the necessary structural features to serve as a precursor to a variety of novel heterocyclic carbenium ions. Hence, the six *ortho* methoxy groups may serve as leaving groups in one, two, or three double S_NAr reactions with primary amines which would lead to the formation of nitrogen bridges (Scheme 1).



Scheme 1. S_NAr reaction of **1**-BF_4 with excess of primary amines; **a**: R = methyl, $X^- = PF_6^-$; **b**: R = *n*-propyl, $X^- = BF_4^-$.

At the same time the steric bulk of the methoxy groups protects the central carbon atom in cation **1** from nucleophilic addition, which otherwise would lead to the unreactive leuco adduct. Thus, we expected **1** to be an ideal starting material for exploring the *ortho* S_NAr reactions of triaryl carbenium ions. We found that the *ortho* methoxy groups in carbenium ion **1** do undergo substitution upon treatment with primary amines, as outlined in Scheme 1.

The reaction proceeds in a stepwise manner, thus we could isolate the partially substituted compounds **2a**-PF_6 and **3b**-BF_4 (in good yields) when the reaction was performed overnight at room temperature and at 100 °C for 45 min, respectively. The hexafluorophosphate salt of the 4,8,12-trimethyl-4,8,12-triazatriangulenium ion **4a** was obtained in 59% yield after heating a solution **1** with excess methylamine to reflux in *N*-methylpyrrolidine (NMP) for 10 h; benzoic acid was added to raise the reflux temperature of the reaction mixture.

Several attempts were made to collect X-ray diffraction data on the very thin needlelike orange-red crystals of **4a**-PF_6; unfortunately the crystals scattered the X-rays very poorly and no true Bragg peaks were observed. However, on Weissenberg-oscillation films[12] scattered intensity was observed in bands which correspond to a direct lattice translation of 3.5 Å, and could result from a stacked formation of **4a**. Whereas our structural studies of the pure oxygen analogues (trioxatriangulenium salts, TOTA) showed that these cations never stack in the solid state,[13] there is one example of an amino-substituted triangulene that forms cationic stacks.[8] Thus, it is likely that **4a**, because of its pronounced charge delocalization, has the ability to form cationic stacks in the crystalline state. We showed that the disc-shaped cations in TOTA might rotate in the solid state at elevated temperature.[13] In **4a** the methyl substituents make the structure more disclike than for TOTA (see Figure 1), thus molecular rotation (dynamic or static) in the solid state may explain the disorder in the crystals of **4a**.

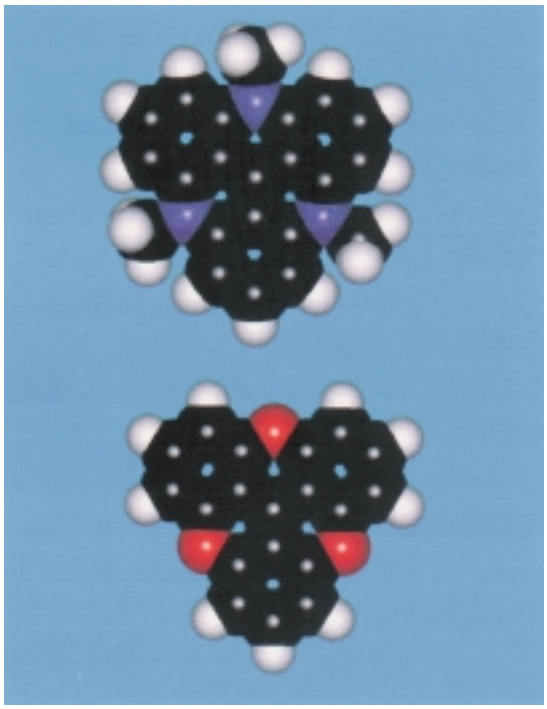


Figure 1. Space-filling models of the cations **4a** (top) and TOTA (below). The models were generated by AM1 calculations, the structure of the TOTA cation is in good agreement with the X-ray structure.

As a measure of the thermodynamic stability of the triazatriangulenium system, the pK_{R^+} value of compound **4a** was determined by use of the C_- acidity function;[14] measurements were made by UV/Vis spectroscopy in a DMSO/water/tetramethylammonium hydroxide solvent system. Although the titration displayed nonideal behavior, the pK_{R^+} value was estimated at 23.7(±0.2).[15] This result indicates that the introduction of three nitrogen bridges into the triangulenium skeleton raises the stability by 14 orders of magnitude relative to the known oxygen analogue TOTA ($pK_{R^+} = 9.1$),[11] and underlines the unique stabilizing power of nitrogen bridges in heterocyclic carbenium salts. The extremely high stability of **4a** places this triazatriangulenium cation among the most stable carbenium ions.[7]

Significant changes in the electronic absorption spectra of the cationic chromophores follows each substitution. The absorption spectra of the three new nitrogen-bridged heterocycles **2a**, **3b**, and **4a** are shown in Figure 2. The first ring closure converts a triaryl methane dye **1**[16] into an acridinium system **2** (Scheme 1) which has a broad and structured low-intensity absorption in the visible region of the UV/Vis spectrum. Formation of the second nitrogen bridge causes a red shift of this band by almost 100 nm and a threefold

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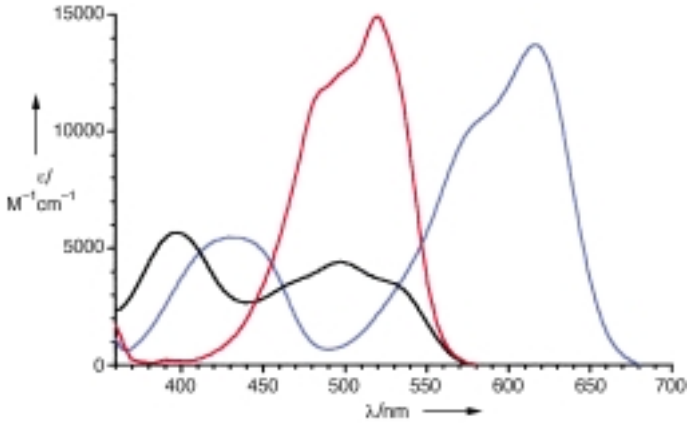

Figure 2. Absorption spectra of **2a**-PF_6 (black), **3b**-BF_4 (blue), and **4a**-PF_6 (red) in acetonitrile.

increase in the extinction coefficient. These effects can be attributed to the enlargement and twisting[17] of the chromophoric system.[18] The formation of the last nitrogen bridge gives the triazatriangulenium system **4**; the increased symmetry and planarity of this system results in a significant blue shift and narrowing of the low-energy absorption band.

In conclusion, the synthetic strategy based on the S_NAr reaction of **1**-BF_4 with primary amines provides a facile tool for the construction of new extended heterocyclic carbenium ions.

Experimental Section

2a-PF_6: Methylamine (5 mmol) in NMP (1 mL) was added to compound **1**-BF_4 (1.0 g, 2 mmol) dissolved in NMP (20 mL). After 20 h at room temperature the reaction mixture was poured into an aqueous KPF_6 solution (100 mL, 0.2 M), acidified with HPF_6 (60%, 1 g, 4 mmol), the precipitate was collected by filtration and washed thoroughly with water. Recrystallization from methanol gave **2a**-PF_6 as dark red needles (0.82 g, 78%). ^{1}H NMR ([D$_3$]MeCN): $\delta = 8.23$ (dd, $J = 8.1$, 9.1 Hz, 2H), 7.96 (d, $J = 9.1$ Hz, 2H), 7.47 (t, $J = 8.4$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 6.81 (d, $J = 8.4$ Hz, 2H), 4.64 (s, 3H), 3.58 (s, 6H), 3.57 (s, 6H); ^{13}C NMR ([D$_3$]MeCN): $\delta = 160.80$, 157.52, 156.17, 142.92, 140.05, 129.83, 120.15, 119.90, 109.98, 106.87, 104.11, 57.17, 56.04, 40.82; MS (MALDI-TOF): m/z: 390 [M^+]; UV/Vis (MeCN), λ_{max}(nm, (lg ε)) = 525sh (3.56), 497 (3.65), 395 (3.75), 358 (3.37), 340 (3.06), 285 (4.86); elemental analysis calcd for $C_{24}H_{24}NO_4PF_6$ (%): C 53.83, H 4.48, N 2.61; found: C 53.83, H 4.33, N 2.59.

3b-BF_4: *n*-Propylamine (5.0 g, 85 mmol) was added to a solution of compound **1**-BF_4 (1.75 g, 3.4 mmol) in NMP (30 mL). The reaction mixture was heated to reflux (100–110 °C) for 45 min. The crude product precipitated on addition of water. Recrystallization from acetonitrile/ethanol gave **3b**-BF_4 as dark blue crystals (1.31 g, 77%). ^{1}H NMR ([D$_3$]MeCN): $\delta = 8.20$ (t, $J = 8.6$ Hz, 1H), 7.93 (t, $J = 8.5$ Hz, 2H), 7.57 (d, $J = 8.6$ Hz, 2H), 7.52 (d, $J = 8.9$ Hz, 2H), 6.95 (d, $J = 8.0$ Hz, 2H), 4.66 (m, 2H), 4.42 (m, 2H), 3.76 (s, 6H), 2.10 (m, 4H), 1.23 (t, $J = 7.4$ Hz, 6H); ^{13}C NMR ([D$_3$]MeCN): $\delta = 159.51$, 142.39, 141.91, 138.76, 136.82, 136.27, 119.21, 112.79, 107.40, 104.81, 102.81, 55.37, 51.12, 19.34, 10.07; MS (MALDI-TOF): m/z: 413 [M^+]; UV/Vis (MeCN), λ_{max} (nm, (lg ε)) = 616, (4.14), 582sh (4.02), 429 (3.74), 350sh (3.44), 334 (3.71), 310 (4.65); elemental analysis calcd for $C_{27}H_{29}N_2O_2BF_4$ (%): C 64.82, H 5.80, N 5.60; found: C 64.83, H 5.77, N 5.55.

4a-PF_6: Benzoic acid (6.2 g, 51 mmol) and methylamine (50 mmol) in NMP (10 mL) were added to a solution of compound **1**-BF_4 (1.0 g, 2.0 mmol) in NMP (12 mL). The reaction flask was fitted with a dry ice condenser and heated to reflux under argon for 10 h. Twice during the reaction extra methylamine (2 × 5 mmol) was added. Workup as for **2**-PF_6 followed by recrystallization from acetonitrile and pyridine gave **4a**-PF_6 as red needles (0.56 g, 59%). ^{1}H NMR ([D$_3$]MeCN): $\delta = 7.74$ (t, $J = 8.6$ Hz, 3H), 6.75 (d, $J = 8.6$ Hz, 6H), 3.21 (s, 9H); ^{13}C NMR ([D$_3$]MeCN): $\delta = 139.61$, 138.02, 137.27, 108.32, 104.96, 34.67; MS (MALDI-TOF): m/z: 324 [M^+]; UV/Vis (MeCN), λ_{max} (nm, (lg ε)) = 519 (4.17), 498sh (4.10), 487sh (4.07), 350 (3.80), 290sh (4.32), 272 (5.05); elemental analysis calcd for $C_{22}H_{18}N_3PF_6$ (%): C 56.29, H 3.84, N 8.95; found: C 56.56, H 3.91, N 8.97.

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[1] D. F. Duxbury, *Chem. Rev.* **1993**, *93*, 381–433.
[2] K. H. Drexhage in *Dye Lasers* (Ed.: F. P. Schäfer), Springer, **1990**, pp. 155–200.
[3] R. P. Haugland, *Handbook of Fluorescent Probes and Research Chemicals*, 6th ed., Molecular Probes, Eugene, **1996**.
[4] H. H. Freeman in *Carbonium Ions* (Eds.: G. A. Olah, P. v. R. Schleyer), Wiley-Interscience, New York, **1973**, Chap. 28.
[5] E. M. Arnett, R. A. Flowers II in *Stable Carbocation Chemistry* (Eds.: G. K. Surya Prakash, P. von R. Schleyer), Wiley, Chichester, **1997**, pp. 265–296.
[6] K. Komatsu, H. Akamatsu, Y. Jinbu, K. Okamoto, *J. Am. Chem. Soc.* **1988**, *110*, 633–634.
[7] S. Ito, S. Kikuchi, N. Morita, T. Asao, *J. Org. Chem.* **1999**, *64*, 5815–5821.
[8] B. W. Laursen, F. C. Krebs, M. F. Nielsen, K. Bechgaard, J. B. Christensen, N. Harrit, *J. Am. Chem. Soc.* **1998**, *120*, 12255–12263.
[9] M. Wada, T. Watanabe, S. Natsume, H. Mishima, K. Kirishima, T. Erabi, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3233–3240.
[10] L. Teruel, Ll. Viadel, J. Carilla, Ll. Fajari, E. Brillas, J. Sane, J. Rius, L. Juliá, *J. Org. Chem.* **1996**, *61*, 6063–6066.
[11] J. C. Martin, R. G. Smith, *J. Am. Chem. Soc.* **1964**, *86*, 2252–2256.
[12] Crystals were mounted and aligned optically along the longest axis of the crystal. Weissenberg-oscillation photographs were recorded by using filtered $Cu_{K\alpha}$ radiation with rotation through ±100° and an exposure time of 24 h. This resulted in darkened films but the bands of scattered intensity were clearly visible.
[13] F. C. Krebs, B. W. Laursen, I. Johansen, A. Faldt, K. Bechgaard, C. S. Jacobsen, N. Thorup, K. Boubekeur. *Acta Crystallogr. Sect. B* **1999**, *55*, 410–423.
[14] The procedure used was analogous to that reported in ref. [8] except for fitting of the C_- and H_- scales, where 7th order polynomiums was used instead of 3rd order polynomiums. The acidity functions C_- and H_- express the change in activity of OH^- towards carbenium ions and the change in activity of OH^- towards acidic protons, respectively.
[15] The slope of lg([ROH]/[R$^+$]) versus C_- was found to be 0.85 and not the ideal value of 1.0; however, even if this change in the C_- function begins just above the previous calibrated region (below 70 mol% DMSO, ref. [8]) a maximum decrease in the pK_{R^+} value of 0.5 pK_{R^+} units, relative to the measured value of 23.9, is obtained.
[16] A discussion of a very different type of triaryl methane chromophore is found in ref. [11].
[17] NMR spectra and molecular modeling of **3b** suggests that because of the steric repulsion between the two methoxy groups it exists in a twisted helical conformation.
[18] J. Griffiths, *Colour and Constitution of Organic Molecules*, Academic Press, London, **1976**.

  0044-8249/00/11219-3576 $ 17.50+.50/0