$[Cu_3(H_2L3)(NO_3)](NO_3)(dmf)_4{\cdot}H_2O$ (**2**·4 dmf·H_2O). A mixture of $Cu(NO_3)_2{\cdot}6H_2O$ (0.321 g, 1.08 mmol) and dhtmb (0.20 g, 0.543 mmol) in dry ethanol (80 mL) were heated to reflux for 10 min and a solution of 1,3-diaminopropan-2-ol (0.052 g, 0.543 mmol) in dry methanol (20 mL) added dropwise. The emerald green solution darkened as reflux was continued for 2 h. the mixture was filtered, cooled, and concentrated under vacuum where upon a green solid precipitated (analyzed as $[Cu_4(H_4L)(NO_3)(OH)_2(H_2O)_4]$). This complex was dissolved in DMF and the color changed to brown; crystals of the trinuclear complex **2**·3 dmf were obtained in 40% yield by diffusion of diethyl ether into the solution. Elemental analysis calcd (%) for **2**·4 dmf·H_2O: C 51.8, H 6.4, N 9.4; found: C 52.1, H 6.5, N 9.4. Crystal dimensions: $0.45 \times 0.24 \times 0.04$ mm^3, monoclinic, space group $P2_1/c$, $a = 17.234(1)$, $b = 22.130(2)$, $c = 17.658(1)$ Å, $\beta = 103.488(1)°$, $V = 6549.0(8)$ Å^3, $\rho_{calcd} = 1.395$ Mg m^{-3}. 46 309 reflections, 11 521 independent ($R_{int} = 0.0424$), $\mu = 1.036$ mm^{-1}, $T_{max} = 1.000$, $T_{min} = 0.885$; 859 least-squares parameters $R1 = 0.0646$ $wR2 = 0.1638$ (2σ data).

$[Cu_4(H_2L3)(OH)_2(sol)_2](NO_3)_2$ (**3**·2 H_2O where sol = water or ethanol). A mixture of $Cu(NO_3)_2{\cdot}6H_2O$ (0.16 g, 0.543 mmol) and dhtmb (0.20 g, 0.543 mmol) in dry ethanol (70 mL) was heated to reflux for 10 min and a solution of 1,3-diaminopropan-2-ol (0.052 g, 0.543 mmol) in dry methanol (20 mL) added dropwise. The solution changed to emerald green and darkened as reflux was continued for 1 h. The solution was cooled, filtered, and evaporated to dryness. The residue was then dissolved in dichloromethane, filtered, and evaporated again before being dissolved in ethanol. Green $[Cu_4(H_2L3)(OH)_2(H_2O)_2](NO_3)_2{\cdot}2H_2O$ was obtained from this solution in 79% yield. Elemental analysis calcd (%) for **3**·2 H_2O: C 47.1, H 5.6, N 6.3; found: C 47.1, H 5.5, N 6.3. Crystals of $[Cu_4(H_2L3)(OH)_2(H_2O)(EtOH)](NO_3)_2{\cdot}2EtOH{\cdot}H_2O$ (**3**·2 EtOH·H_2O) were obtained by slow evaporation of a solution of **3**·2 H_2O in an ethanol/benzene/petroleum ether mixture. Crystal dimensions: $0.31 \times 0.13 \times 0.04$ mm^3, monoclinic, space group $P2_1/c$, $a = 11.867(2)$, $b = 14.125(3)$, $c = 41.220(7)$ Å, $\beta = 93.406(3)°$, $V = 6897(2)$ Å^3, $\rho_{calcd} = 0.352$ Mg m^{-3}. 47 670 reflections, 12 095 independent ($R_{int} = 0.0902$), $\mu = 1.285$ mm^{-1}, $T_{max} = 1.000$, $T_{min} = 0.766$; 696 least-squares parameters $R1 = 0.0763$ $wR2 = 0.21.19$ (2σ data). The uncoordinated solvate molecules and nitrate ions were highly disordered and were treated using the SQUEEZE program[10] (see the Supporting Information).

X-ray data were collected at 150(2) K on a Bruker SMART 1000 diffractometer using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) to $2\theta_{max}$ of 25°. The structures were solved by direct methods and refined on F^2 using all the data.[11] Non-hydrogen atoms were refined with anisotropic ADPs and hydrogen atoms attached to full-occupancy carbon atoms were inserted at calculated positions. Details concerning treatment of disorders and of hydrogen atoms not bonded to carbon atoms are described in the Supporting Information. CCDC 190246.(**1**·1.6 Et_2O·EtOH) CCDC 190247 (**2**·3 dmf), and CCDC 190248 (**1**·2 H_2O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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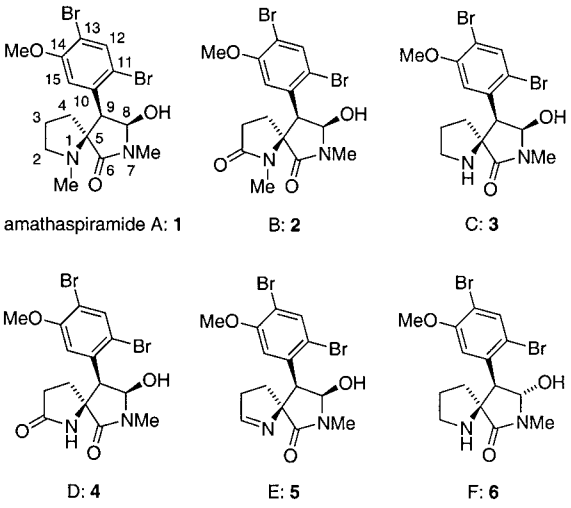
The Total Synthesis of (−)-Amathaspiramide F**

Chambers C. Hughes and Dirk Trauner*

The amathaspiramides A–F (**1**–**6**) are a family of marine alkaloids recently isolated from a New Zealand collection of the bryozoan *Amathia wilsoni*.[1,2] Marked by a dense array of polar functionality, the natural products feature a novel



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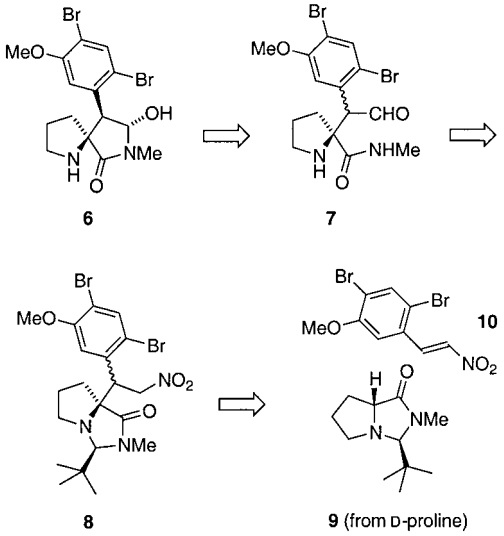
spirobicyclic core consisting of pyrrolidine and pyrrolidinone rings and an unusual dibromomethoxyphenyl ring. Their structures and absolute configurations were established by anomalous X-ray diffraction of amathaspiramide F and extensive NMR studies. Though several of the amathaspiramides are moderately cytotoxic or show antiviral and antibiotic properties, they attracted our attention mostly due to their intriguing molecular architecture. We now report the first total synthesis of a member of this family, amathaspiramide F (**6**).

Our synthetic program provided an opportunity to showcase Seebach's concept of "self-regeneration of stereochemistry (SRS)",[3] a method for the asymmetric α alkylation of amino acids that has been widely exploited in the preparation of novel amino acids and peptidomimetics and in the total synthesis of several natural products.[4]

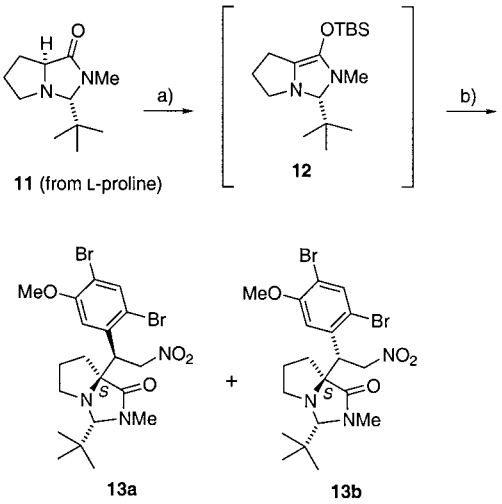
Retrosynthetically, disconnection of the *N*-acyl hemiaminal function in amathaspiramide F (**6**) leads to the amino aldehyde **7**, which can be traced back to the nitroalkyl compound **8** via Nef reaction and engagement of the aldehyde and amide function in a cyclic acetal (Scheme 1). We reasoned that this key intermediate could be derived from *N*,*N*-acetal **9**



Scheme 1. Retrosynthetic analysis of amathaspiramide F.

by conjugate addition of its lithium enolate to the nitrostyrene derivative **10**.[5] The *N*-methyl moiety of the final product would thus be introduced at an early stage of the synthesis. Following ample precedence given by Seebach and others, the alkylation of **9** should proceed under retention of configuration. In other words, the substituent replacing the bridgehead hydrogen atom would reside *cis* with respect to the *tert*-butyl group ("*cis* rule"). We were not particularly concerned about the stereochemical outcome of the conjugate addition with respect to the benzylic stereocenter at C9. Given its position next to a masked carbonyl group, the aryl ring would probably adopt the thermodynamically most stable configuration in the final product.

According to this retrosynthetic analysis, the synthesis of natural 5*S*-configured amathaspiramide F (or C) would require an acetal derived from D-proline as starting material. Because of the relatively high cost of D-proline, however, we decided to first use its cheaper enantiomer, aiming at a synthesis of nonnatural (+)-amathaspiramide F. Our synthesis therefore started with the known *N*,*N*-acetal **11**,[6] the alkylation of which has not been previously reported (Scheme 2). Initial attempts to alkylate **11** were unsuccessful since the α position proved difficult to deprotonate. Fortu-



Scheme 2. Reagents and conditions: a) 1. *t*BuLi, HMPA, THF, −78 °C→RT; 2. TBSCl, 0 °C; b) 1. **10**, −78 °C; 2. $MgBr_2 \cdot OEt_2$, −78 °C→RT, 72 %, 10:1 (**13a**:**13b**) mixture of diastereomers. HMPA = hexamethylphosphoramide, TBSCl = *tert*-butyldimethysilyl chloride.

nately, in the presence of HMPA, the desired enolate could be cleanly generated using *tert*-butyllithium. Simple addition of nitro olefin **10**[7] to this enolate, however, resulted in the formation of a complex mixture with no detectable trace of the desired product. This difficult conjugate addition was finally realized when the silyl ketene acetal **12** was generated in situ and reacted with the nitro olefin in the presence of $MgBr_2 \cdot OEt_2$.[8] A 10:1 mixture of diastereomers **13a** and **13b** was thus obtained (see *Experimental Section*).

To our surprise, however, the two diastereomers **13a** and **13b** turned out to be both *S*-configured at the newly formed quaternary center. This fortuitous violation of the *cis* rule was confirmed by an X-ray analysis of the major diastereomer **13a** (Figure 1).[9,10] Remarkably, both the quaternary and the benzylic stereocenter in **13a** correspond to the natural amathaspiramide series.

According to literature precedence[3b] and our own calculations, the bicyclic silyl ketene acetal **12** adopts a cup-shaped conformation wherein the two nitrogen atoms are pyramidalized and the *tert*-butyl group resides on the convex side of the bicycle (Scheme 3). Conventionally, the alkylation would proceed from this side as well. However, in **12** the bulky TBS substituent is also oriented towards the convex side of the diazabicyclo[3.3.0]octene framework, considerably crowding the corresponding diastereoface of the nucleophilic double bond. Apart from this ground state argument, unfavorable torsional interactions between the *N*-methyl group and the OTBS substituent may occur in a transition state leading to the *cis* product (**14b**). Hence the alkylation takes place from

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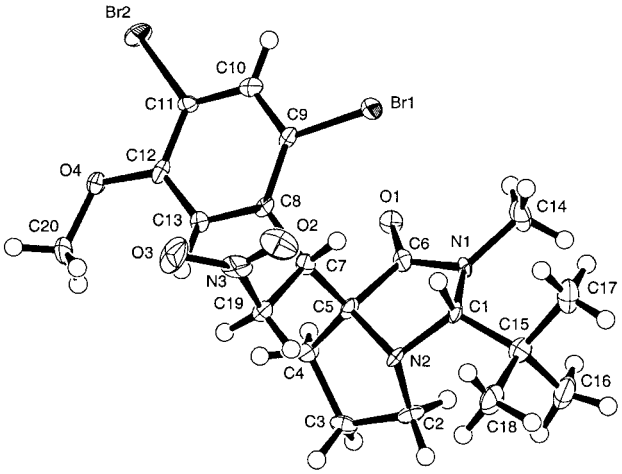
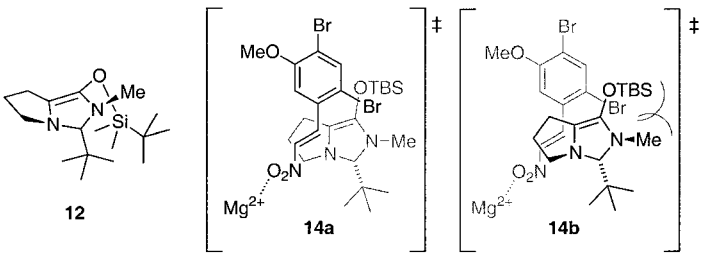


Figure 1. Molecular structure of **13a**.

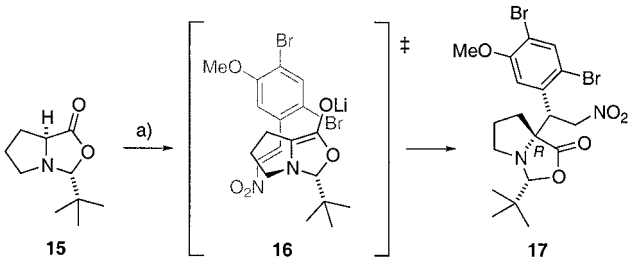


Scheme 3. Stereochemical rationale for the preferred formation of diastereomer **13a**.

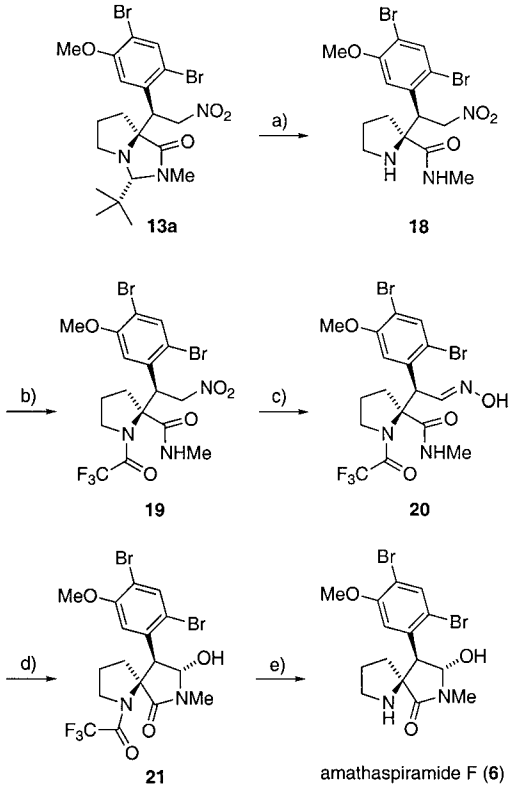
the opposite side, via **14a**, resulting in *trans* substitution with inversion of the stereocenter (Scheme 3). The high simple diastereoselection (10:1 in favor of **13a**) can be explained by invoking an open transition state with the dibrominated phenyl ring oriented away from the bicyclic component.

Supporting this stereochemical rationale, the well-precedented alkylation of *N,O*-acetal **15**[3a] afforded the expected 5*R-cis* product **17**[10] as the only isolated diastereomer (Scheme 4). In this case, the reaction presumably proceeds through the open transition state **16**.

Having quickly assembled the carbon skeleton of the amathaspiramides, we turned our attention toward the formation of the missing heterocyclic ring. The completion of the synthesis required cleavage of the acetal, conversion of the primary nitro group to an aldehyde via a Nef reaction[11] (or its equivalent), and subsequent cyclization to yield amathaspiramide F. Though the hydrolysis of the *N,N*-acetal was achieved without difficulties (Scheme 5), direct implementation of the Nef reaction proved problematic. Starting from either acetal **13a** or its hydrolysis product **18**, no aldehyde or cyclized product could be obtained under a variety of hydrolytic or oxidative conditions.[12]



Scheme 4. Reagents and conditions: a) 1. LDA, THF, −78 °C; 2. **10**, −78 °C→−30 °C, 18 %. LDA = lithium diisopropylamide.



Scheme 5. Reagents and conditions: a) 4 M H_2SO_4, THF, RT, 86 %; b) 1. TFAA, py, CH_2Cl_2, 0 °C; 2. MeOH, 0 °C→RT, 98 %; c) $SnCl_2$, PhSH, Et_3N, MeCN, RT, 85 %; d) IBX, THF, DMSO, RT, 65 %; e) $LiBH_4$, THF, 0 °C→RT, 80 %. TFAA = trifluoroacetic anhydride, IBX = 1-hydroxy-1,2-benziodoxol-3(*1H*)-one-1-oxide.

Since all attempts to convert the nitro group into the aldehyde in the presence of a free secondary amine failed, we reluctantly resorted to protecting group manipulations. Recently, the trifluoroacetyl function has emerged as a useful protecting group for sterically hindered amines,[13] for example, those attached to a quaternary center. Accordingly, **18** was treated with trifluoroacetic anhydride to afford **19** (Scheme 5). With the basic nitrogen thus protected, **19** could be efficiently converted to oxime **20** following a protocol described by Bartra et al.[14] Hydrolysis of the oxime with concomitant cyclization was then achieved with a hypervalent iodine reagent (IBX)[15] to afford *N*-trifluoroacetyl amathaspiramide F (**21**).[16] Notably, no formation of the diastereomer corresponding to amathaspiramide C was observed under these conditions. Finally, amathaspiramide F (**6**) was obtained upon treatment of **21** with lithium tetrahydroborate in THF.[17] The spectra of our synthetic material (NMR, IR, MS) closely match the ones published for the natural product,[1] and the optical rotation of our sample ($[\alpha]_D^{25} = -41.0$, $c = 0.50$, MeOH; ref. [1]: $[\alpha]_D = -10$, $c = 0.0023$, MeOH) confirmed the absolute configuration of our synthetic amathaspiramide F.[18]

In summary, a highly stereocontrolled total synthesis of (−)-amathaspiramide F was achieved in six steps starting

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from the known acetal **11**. The synthesis features a remarkable exception to the well-established *cis* rule governing SRS chemistry, reaffirming that subtle changes in the substrate can lead to dramatically different stereochemical outcomes. It also presents an efficient method for circumventing a problematic Nef reaction in the presence of densely spaced polar functionality. Studies toward the synthesis of other members of the amathaspiramide family, particularly amathaspiramides C and E, are underway and will be reported in due course.

Experimental Section

To amide **11** (235 mg, 1.19 mmol) in THF (4.0 mL) at −78 °C a solution of *t*BuLi in pentane (0.88 mL, 1.5 M, 1.3 mmol) was added dropwise using a syringe. After 10 min HMPA (250 μL, 1.44 mmol) was added by syringe, and after additional 10 min the solution was allowed to warm to room temperature over 1 h. The solution was then cooled to 0 °C, and TBSCl (218 mg, 1.44 mmol) in THF (1.0 mL) was added dropwise using a cannula. After 1 h at 0 °C the solution was cooled to −78 °C, and nitroalkene **10** (485 mg, 1.44 mmol) in THF (7.0 mL) was added dropwise by cannula. Immediately, $MgBr_2{\cdot}OEt_2$ (372 mg, 1.44 mmol) was added in one portion. The reaction mixture was maintained at −78 °C for 2 h then allowed to warm to room temperature over 10 h. The solution was poured into saturated $NaHCO_3$ solution (200 mL) and extracted five times with CH_2Cl_2 (100 mL). The combined organic layers were washed once with brine (100 mL), dried, filtered, and concentrated. The product was purified by column chromatography (40 % EtOAc in hexanes) to afford 459 mg (72 %) of **13a/b** as a white solid. The major diastereomer **13a** could be purified by recrystallization from CH_2Cl_2/hexanes. The crystals obtained had a clear, columnar appearance distinct from the yellow, blocky appearance of the minor diastereomer **13b**.

13a: $[\alpha]_D^{25} = -21.7$ ($c = 1.00$, $CHCl_3$); mp: 198–200 °C; IR (KBr): $\tilde{\nu} = 2966$, 1694, 1549, 1476, 1368, 1251, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.73$ (s, 1H), 6.78 (s, 1H), 4.97 (dd, $J = 13.5$, 5.5 Hz, 1H), 4.82 (dd, $J = 13.5$, 9.5 Hz, 1H), 4.53 (dd, $J = 9.5$, 5.5 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 1H), 3.07 (m, 1H), 2.88 (s, 3H), 2.78 (m, 1H), 2.01–2.11 (m, 2H), 1.67–1.82 (m, 2H), 1.12 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 177.5$, 155.6, 136.9, 135.8, 117.7, 112.4, 111.0, 83.6, 76.7, 75.4, 56.7, 49.5, 44.6, 33.4, 30.8, 30.6, 25.3 ppm; HRMS (FAB$^+$): $m/z(M-H^+)$: calcd for $C_{20}H_{28}{}^{79}Br^{81}BrN_3O_4$: 534.0426; found: 534.0417.

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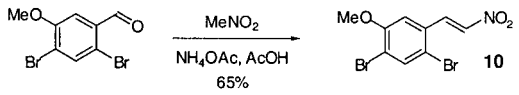

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[9] The stereochemistry of **13a** and **13b** was further substantiated by NOE's observed between the acetalic proton and benzylic protons in both isomers.

[10] All X-ray measurements were made on a SMART CCD area detector with graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). **13a** ($C_{20}H_{27}Br_2N_3O_4$): crystal dimensions $0.32 \times 0.21 \times 0.13$ mm, monoclinic, space group $P2_1$, $a = 14.5715(4)$, $b = 7.7135(1)$, $c = 20.3642(5)$ Å, $\beta = 108.981(1)^\circ$, $V = 2164.43(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.633$ g cm^{-3}, $2\theta_{max} = 49.4^\circ$, $T = 138$ K, 9660 measured reflections, 4007 independent reflections ($R_{int} = 0.061$), data were corrected for Lorentz and polarization effects, $\mu = 37.88$ cm^{-1}, $[\delta/\sigma]_{max} = 0.00$, 522 parameters refined, $R = 0.037$ (for 4982 reflections with $I > 3.00\sigma(I)$), $R_w = 0.043$, max./min. residual peaks in the final difference map 0.35/−0.53 e Å^{-3}. **17** ($C_{19}H_{24}Br_2N_2O_5{\cdot}0.5\,CH_2Cl_2$): crystal dimensions $0.22 \times 0.20 \times 0.07$ mm, orthorhombic, space group $P2_12_12_1$, $a = 9.1876(8)$, $b = 16.632(2)$, $c = 30.276(3)$ Å, $V = 4626.3(7)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.619$ g cm^{-3}, $2\theta_{max} = 46.5^\circ$, $T = 138$ K, 18751 measured reflections, 3963 independent reflections ($R_{int} = 0.108$), data were corrected for Lorentz and polarization effects, $\mu = 36.62$ cm^{-1}, $[\delta/\sigma]_{max} = 0.01$, 532 parameters refined, $R = 0.040$ (for 4202 reflections with $I > 3.00\sigma(I)$), $R_w = 0.044$, max./min. residual peaks in the final difference map 0.32/−0.43 e Å^{-3}. CCDC-188930 (**13a**) and CCDC-192396 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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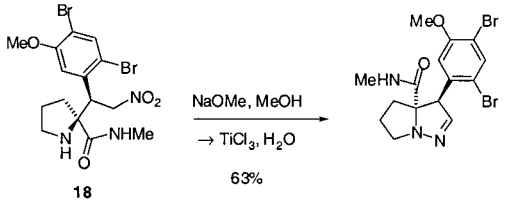
[12] Nevertheless, some remarkable reactivity was noticed. For instance, when nitro compound **18** was deprotonated to form the corresponding nitronate and then treated with $TiCl_3$, an unexpected cyclization occurred that (to our knowledge) represents a conceptually novel method for synthesizing hydrazones:



[13] For recent applications of the TFA protecting group, see: a) K. C. Nicolaou, B. S. Safina, C. Funke, M. Zak, F. J. Zécri, *Angew. Chem.* **2002**, *114*, 2017 – 2020; *Angew. Chem. Int. Ed.* **2002**, *41*, 1937 – 1940; b) M. W. Carson, G. Kim, M. F. Henteman, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4582 – 4584; *Angew. Chem. Int. Ed.* **2001**, *40*, 4450 – 4452; c) M. W. Carson, G. Kim, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4585 – 4588; *Angew. Chem. Int. Ed.* **2001**, *40*, 4453 – 4456.

[14] M. Bartra, P. Romea, F. Urpi, J. Vilarrasa, *Tetrahedron* **1990**, *46*, 587 – 594.

[15] D. S. Bose, P. Srinivas, *Synlett* **1998**, 977 – 978.

[16] All attempts to perform a one-pot Nef reaction on **19** to afford **21** directly were unsuccessful.

[17] Deprotection with sodium tetrahydroborate in ethanol resulted in significant reduction of the hemiaminal function.

[18] The large discrepancy in value of the optical rotation is perhaps due to the low concentration of the natural sample.

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