Further studies toward himandrine via sequential oxidative amidation – intramolecular Diels–Alder reactions

Takahito Kasahara and Marco A. Ciufolini

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Abstract: Exploratory work toward the alkaloid himandrine evaluated the directing ability of a pyrrolidine C-3 substituent in a diastereotopic group elective intramolecular Diels–Alder reaction of a spirodienone obtained by the oxidative amidation of a phenol. The study also defined a technique for the construction of ring D of the alkaloid.

Key words: alkaloids, Diels–Alder, himandrine, hypervalent iodine, phenols.

Résumé : Des travaux préliminaires en vue de la synthèse de l'alcaloïde himandrine ont permis d'évaluer la possibilité d'un substituant en position C-3 d'une pyrrolidine d'orienter la réaction dans un groupe sélectif diastéréotope, d'une réaction de Diels-Alder intramoléculaire d'une spirodiénone obtenue par amidation oxydante d'un phénol. L'étude a aussi permis de définir une technique pour la formation du cycle D de l'alcaloïde.

Mots-clés : alcaloïdes, Diels-Alder, himandrine, iodure hypervalent, phénols.

[Traduit par la Rédaction]

Introduction

The architecturally interesting alkaloid himandrine (**1**)[1] invites the exploration of an approach that relies on a tandem oxidative amidation[2] – intramolecular Diels–Alder (IMDA)[3] reaction of phenolic sulfonamide **5**. According to the format of Scheme 1, unraveling of the "northeastern" quadrant of **1** produces simplified structure **2**, wherein substituent R and functionality Z would ultimately permit the formation of rings D–F of the natural product. Tricyclic compound **2** could be obtained from **3**, which is the result of an intramolecular Diels–Alder reaction occurring selectively at the pro-S double bond of dienone **4**. The latter is recognized as the product of oxidative cyclization[4] of **5**. Cycloadduct **3** exhibits the incorrect cis configuration of the decaline system relative to **2**, but the neighboring carbonyl group should enable epimerization to the more energetically favorable trans diastereomer.

The expectation that a dienone such as **4** should selectively undergo IMDA in the desired sense was rooted in the surmise that a Diels–Alder reaction occurring at the pro-R double bond (conformer *syn*-**4**, Scheme 2) would be impeded by steric compression between the sulfonyl group and substituents R and $(CH_2)_2Z$ at the C-5 and C-3 position of the pyrrolidine ring, respectively. Conversely, an IMDA reaction occurring at the pro-S double bond (*anti*-**4**) would be relatively free of nonbonding interactions. We describe product **6** as the syn cycloadduct (disfavoured) and compound **3** as the anti cycloadduct (favoured).

It should be noted that the N-bearing tetrasubstituted carbon atom in the dienone segment of compound **4** is chirotopic, but not stereogenic.[5] A generic addition reaction occurring selectively at either the pro-R or the pro-S double bond of the dienone, as exemplified in the conversion of *anti*-**4** to **3**, induces a well-defined configuration, R or S, at the level of the atom in question. The stereocontrolled generation of such tetrasubstituted carbon centers is generally difficult, but approaches based on a selective addition to one of the diastereotopic carbon–carbon π bonds in dienones of type **4** offers a good solution.[6] Of course, the honoree of the present issue of the *Canadian Journal of Chemistry* has contributed significantly to the development of this principle.[7]

A model study designed to address the feasibility of the foregoing tandem sequence employed simplified substrate **7** (Scheme 3),[8] wherein the N-bearing carbon is of opposite configuration relative to the corresponding centre in **4**. The CH_2OH group in **7** correlates with the R substituent in **4**. Relative to the latter, however, the $(CH_2)_2Z$ unit is absent. Oxidative cyclization[2] of **7** with the hypervalent iodine reagent,[9] (diacetoxyiodo)benzene ($PhI(OAc)_2$; DIB), in trifluoroacetic acid (TFA), followed by dilution with toluene and heating at reflux for 12 h, directly afforded the trans-fused compound **10**[10] as the major component of an 8:1 mixture of two cycloadducts.[11] Evidently, epimerization of the primary cycloadduct **9** had occurred in situ, probablybecause of reversible enol formation promoted by TFA. A mere hydroxymethyl

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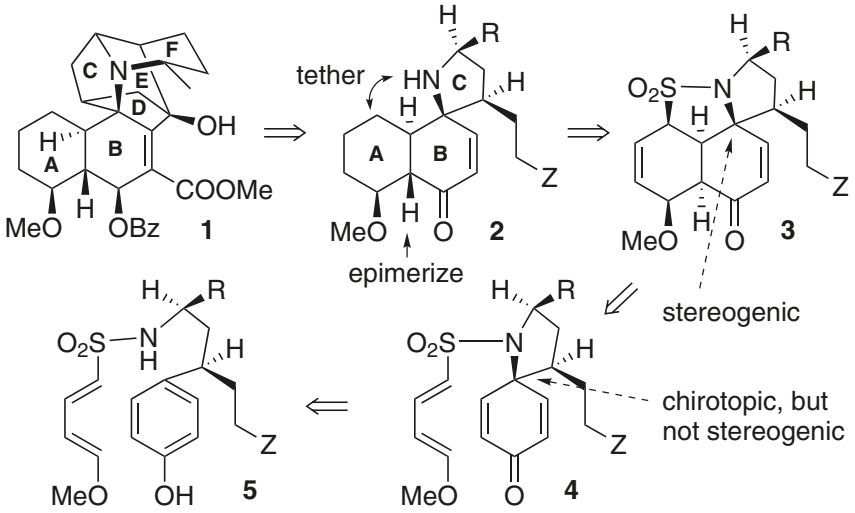
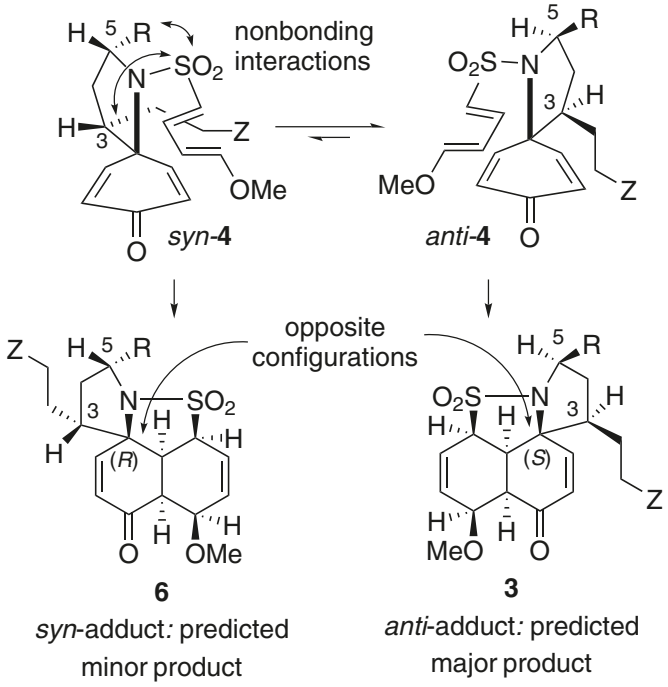
This article is part of a Special Issue dedicated to Professor Derrick Clive. It is a pleasure to dedicate this work to our friend and colleague, Professor Derrick L.J. Clive, in recognition of his many significant contributions to the field of organic chemistry.

Scheme 1.



Scheme 2.



group at the C-5 position of the pyrrolidine moiety of **8** had thus induced a satisfactory degree of diastereoinduction in the cycloaddition step. Our continuing pursuit of himandrine required knowledge of the directing effect of a C-3 group, which would correlate with the $(CH_2)_2Z$ substitution in **4**. Such studies could also define an appropriate functionality Z that might enable the formation of ring D of **1**. Results of investigations in this sense are described herein.

Results and discussion

The present work centred on substrate (±)-**11**, which by analogy with **4** and **7** would be processed through sequential oxidative cyclization and IMDA reactions (Scheme 4). The latter step could produce two pairs of diastereomeric adducts, arising through reaction in an anti (desired) or a syn (undesired) mode with either endo (presumably favoured on electronic grounds) or exo topology. These four compounds are shown in Scheme 4 as structures **13**–**16**. Base-promoted isomerization of **13** and **14** would then provide compound **17**, which possesses the correct relative configuration of all stereocentres as required for himandrine.

A computational study (MM+)[12] carried out with simplified structures **18**–**21**, which lack the *tert*-butyldimethylsiloxy (OTBS) group relative to **13**–**16**, revealed that the pair of endo adducts **18** (an analog of the desired **13**) and **20** (a surrogate of the undesired **15**) are virtually isoenergetic, whereas the anti-exo adduct **19** (cf. the serviceable **14**) was only slightly favoured relative to its diastereomer, **21** (Fig. 1; tabulated energies are relative to the least energetic compound, **18**). This result elicited some apprehension, in that, if the energies of the transition states leading to the various cycloadducts were also to be similar, then the crucial IMDA step would proceed with modest diastereoselectivity. On the other hand, calculations provided support for the prediction that structure **23**, which possesses a himandrine-like relative configuration, should be favoured over its diastereomers **18**–**22** (Fig. 2; tabulated energies are relative to the least energetic isomer, **23**). This boded well for the planned route to compound **17**.

The experimental verification of these hypotheses commenced with a Tozer-type[13] condensation of **24** (the preparation of this material is provided as Supplementary data) with acrolein, followed by selective desilylation of the phenol,[14] leading to dienic sulfonamide **11** (Scheme 5). Oxidative cyclization with DIB in CH_2Cl_2, in the presence of 1.1 equiv of TFA, afforded dienone **12**. Whereas similar dienones had previously been advanced directly to the Diels–Alder step,[8] the present work revealed that greater overall efficiency was attainable by purifying **12** prior to IMDA reaction. When a toluene solution of pure **12** was refluxed for 5 h, an IMDA reaction occurred, which led to a mixture of four compounds. These were ultimately assigned as the anti-endo (**13**), anti-exo (**14**), and syn-endo (**15**) adducts, plus some **17** (i.e., *epi*-**13**).

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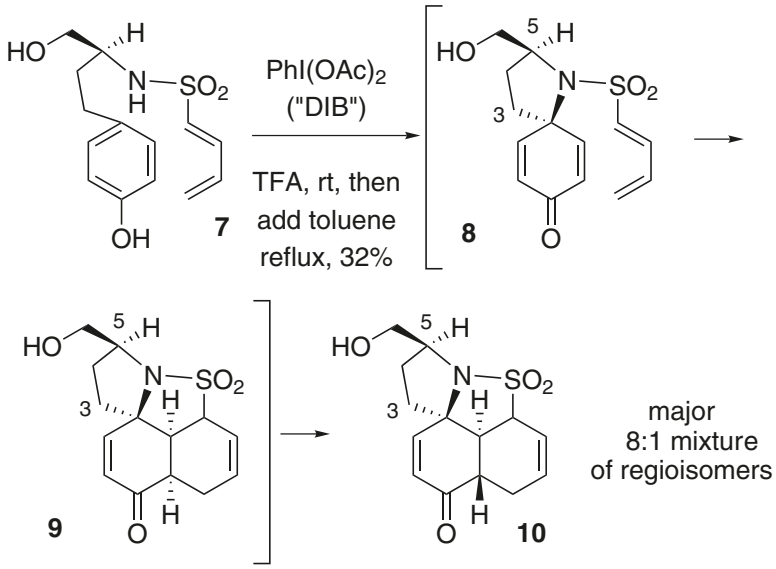
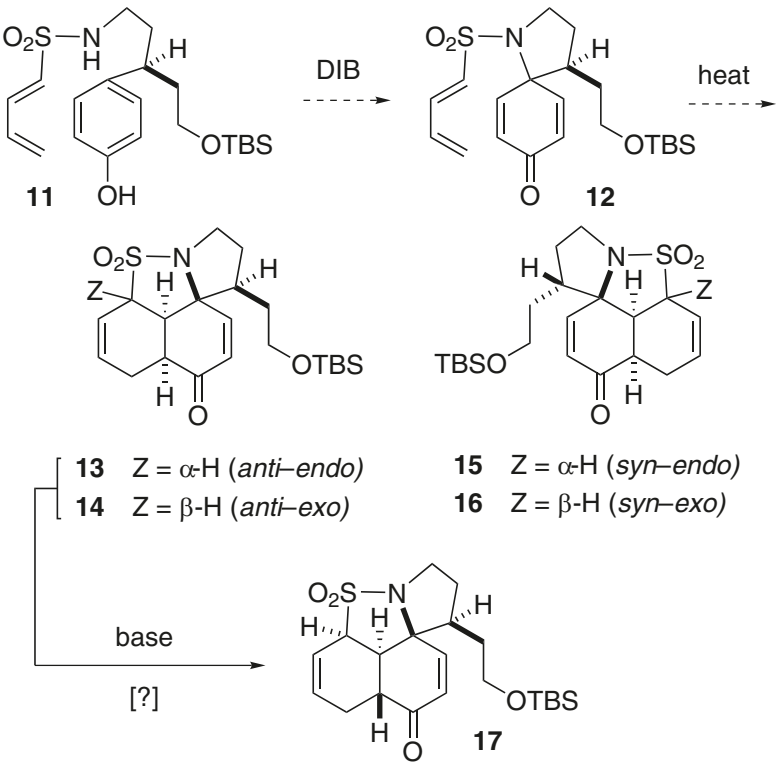
Scheme 3.



Scheme 4.



No evidence could be garnered for the presence of syn-exo cycloadduct **16**. A typical IMDA step would return an approximately 1.2:1.0:1.1 mixture of **13**, **14**, and **15**, respectively, containing a small amount of **17**. The extent of formation of the latter varied from batch to batch of material, and ranged from barely detectable to about 20%–25% of the product mixture. The presence of increased quantities of **17** was always accompanied by a corresponding decrease in **13**. We surmise that trace amounts of residual TFA were responsible for the in situ epimerization of **13** via acid-promoted enol formation. Notice that only **13** can isomerize to **17** under acidic conditions.

As anticipated, the action of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) upon the mixture of IMDA adducts resulted in the conversion of **13** and **14** into the desired **17**, while **15** advanced to **25**. Unsurprisingly, the isomerization of endo-adduct **13** was considerably faster than that of **14**, which also must undergo epimerization at the less

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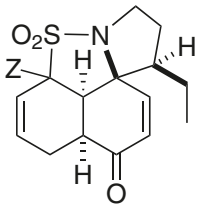
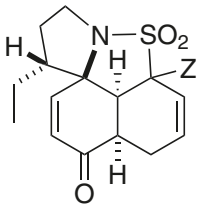
Fig. 1. Estimated energies (MM+, kcal/mol) of model endo and exo adducts **18**–**21** (1 cal = 4.194 J).

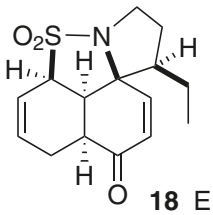




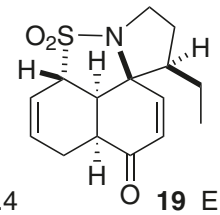
18 Z = α-H (*anti–endo*) E_{conf} = 0.0 **20** Z = α-H (*syn–endo*) E_{conf} = 0.2

19 Z = β-H (*anti–exo*) E_{conf} = 0.4 **21** Z = β-H (*syn–exo*) E_{conf} = 1.4

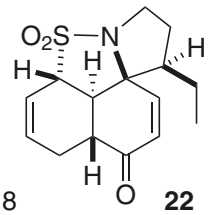
Fig. 2. Estimated energies (MM+, kcal/mol) of *trans*-decalin diastereomers of **18**–**19** (1 cal = 4.194 J).



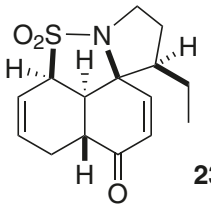
18 E = 4.4



19 E = 4.8



22 E > 10



23 E = 0.0

acidic α position of the sulfonamide. The epimerization step was best carried out in toluene at 60 °C over 2 h, at which time approximately 30% of the starting **13** and **14** remained. Longer reaction times and (or) higher temperatures promoted the formation of two byproducts, assigned as vinylsulfonamides **26** and **27**.[15] Fortunately, the balance of **13** and **14** epimerized to **17** during a subsequent O-deprotection step.

This preliminary phase of our study had determined that a linear alkyl group at the C-3 position of the pyrrolidine is weakly directing compared with a C-5 substituent, favouring the production of anti adducts to the extent of ~2:1. Still, the successful production of compound **17** enabled additional investigations that defined a method for the formation of ring D. To that end, we targeted aldehyde **28** and nitrile **31** (Scheme 6). The aldehyde appeared to be a substrate for cyclization in a hydroacylation (cf. **29**) or a reductive (cf. **30**) mode, whereas the nitrile might advance to **32** through an intramolecular Michael reaction. The aldehyde was secured starting with a tetrabutylammonium fluoride (TBAF) deprotection of **17** (Scheme 7). As alluded to earlier, such a treatment promoted the epimerization of residual **13** and **14** (or desilylated forms thereof). The resultant **33** was contaminated with approximately 15% of epimerized syn adduct **25**.[16] The separation of the two compounds was problematic given their essentially identical mobility on chromatographic supports. Accordingly, the mixture was used as follows in subsequent operations: removal of the undesired regioisomeric material was best achieved at the stage of a more advanced pentacyclic intermediate (vide infra). Dess–Martin oxidation of **33** furnished the requisite **28** in a 72% yield. However, as of this writing we have been unable to achieve cyclization of **28** to either **29** or **30**.

Nitrile **31** was obtained from **33** as outlined in Scheme 8. Again, the final product was contaminated with approximately 15% of an isomer originating from **25**. Attempted base-promoted cyclization of **31** (*t*-BuOK) provided a mixture of uncharacterized products. Suspecting that the problem was due to preferential enolization of the ketone, an event that might trigger numerous undesired side reactions, the cyano group was converted into a more readily enolized aldehyde. The action of diisobutylaluminum hydride (DIBAL) upon **31** induced reduction of the ketone to an alcohol and of the nitrile to an aldehyde, necessitating a subsequent Dess–Martin oxidation to create the desired **35** (also containing ~15% of an isomer derived from **25**). The intramolecular Michael reaction of the latter under basic conditions was still problematic; however, treatment with pyrrolidine triggered cyclization to **36**, presumably through an enamine intermediate (Scheme 9). Separation of isomeric materials emanating from syn adduct **25** was achieved at this stage. However, the final compound was obtained as an essentially 1:1 mixture of epimeric aldehydes. This detracted nothing from the valuable information acquired, i.e., that ring D formation was achievable through the enamine-mediated intramolecular conjugate addition of **35**.

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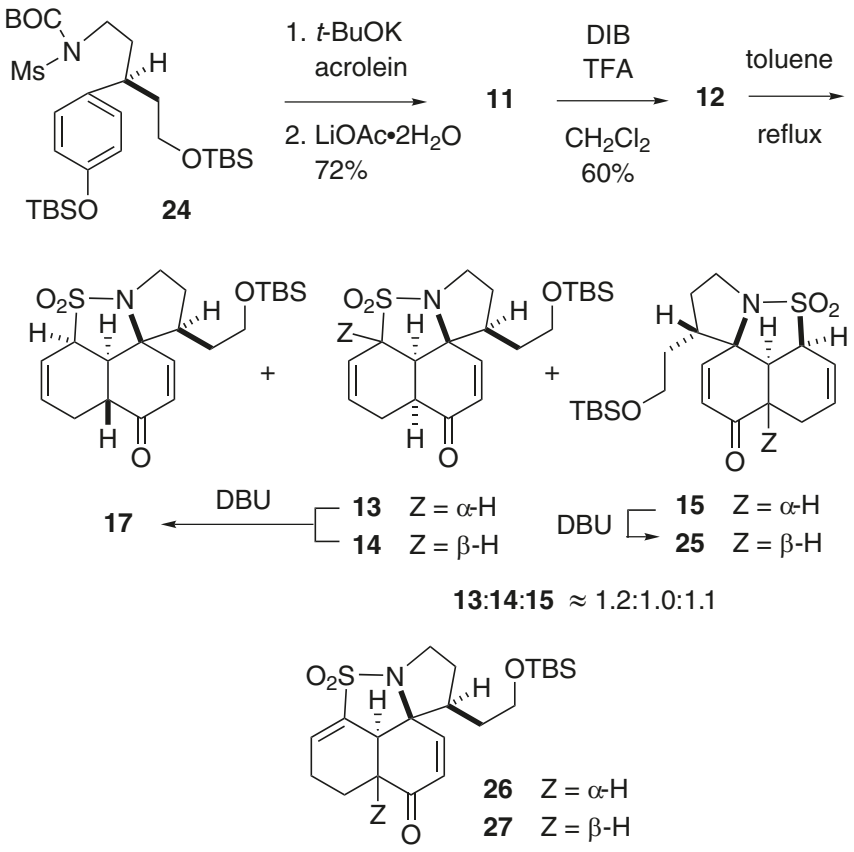
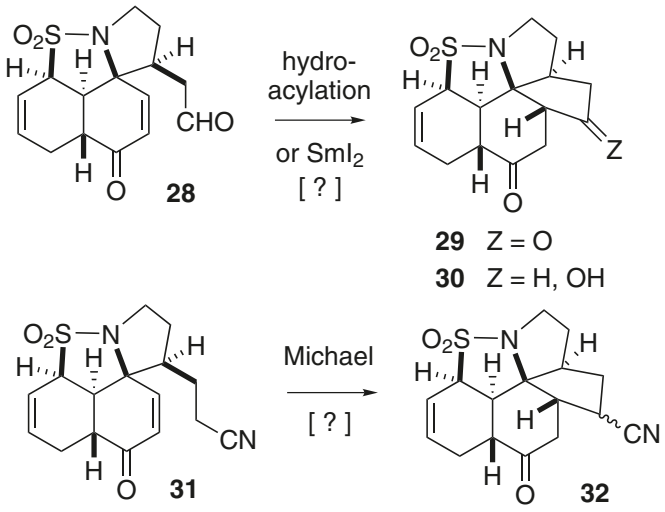
Scheme 5.



Scheme 6.



In summary, exploratory work toward himandrine determined that a C-3 substituent on the pyrrolidine moiety of **12** is weakly anti directing, and that the construction of ring D may be achieved through cyclization of a transient enamine formed in situ from aldehyde **35**. These results are essential to the progress of our ongoing effort toward the natural product. Further results in that sense will be disclosed in due course.

Experimental section

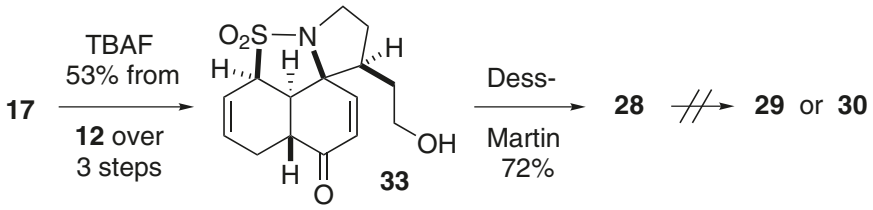
Experimental protocols (additional details are provided as Supplementary data)

Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at room temperature (rt) from $CDCl_3$ solutions. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, *J*, are in hertz (Hz). Multiplicities are reported as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), q (quartet), and m (multiplet), and further qualified as app (apparent) and br (broad). Flash chromatography was performed on 230–400 mesh silica gel.

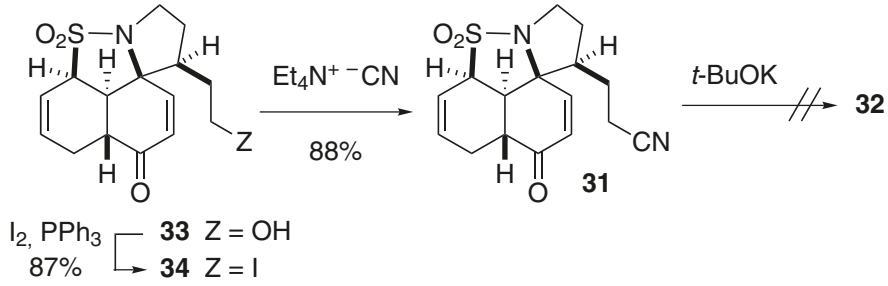
*(1E)-N-1-[[[5-(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[4-(1,1-dimethylethyl)dimethylsilyl]-oxy]-phenyl]pentyl]-1, 3-butadiene-1-sulfonamide (***11***)*

A freshly prepared tetrahydrofuran (THF) solution of KO-*t*-Bu (23 mL, 46 mmol, 2.0 mol/L, 3.5 equiv) was added dropwise to a solution of *N*-Boc sulfonamide **24**[16] (7.94 g, 13.2 mmol, 1.00 equiv) in THF (16 mL) at –78 °C. The resulting pale yellow solution was stirred for 1 h at –78 °C and a solution of acrolein (1.2 mL, 16.1 mmol, 1.2 equiv) in THF (11 mL) was added dropwise. The light green mixture was stirred for 1 h at –78 °C, then gradually warmed up to rt and stirred overnight (12 h). The resulting brown solution was quenched with sat. aq NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The biphasic mixture was filtered through a pad of

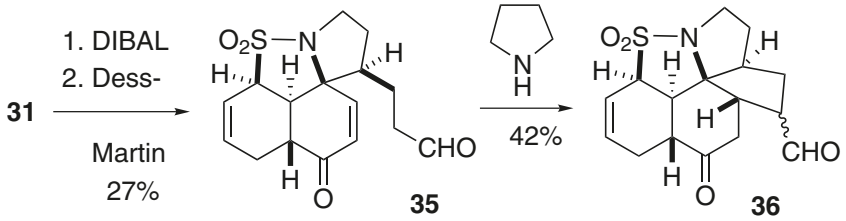
Scheme 7.



Scheme 8.



Scheme 9.



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Celite with EtOAc (60 mL). The mixture was separated and the organic layer was rinsed again with sat. aq NH_4Cl. The combined aqueous phases were extracted twice with EtOAc (10 mL). The organic fractions were combined, rinsed with brine (10 mL), dried (Na_2SO_4), and concentrated to give a brown oil that contained white solids. The crude product was filtered through a pad of Celite with EtOAc (50 mL) and the filtrate was evaporated. To the residual brown oil (6.83 g, 12.7 mmol, 1.0 equiv) in dimethylformamide (DMF; 35 mL) was added $LiOAc{\cdot}2H_2O$ (259 mg, 0.2 equiv) and water (0.72 mL), and stirred at 75 °C for 6 h. The reaction was cooled to rt, diluted with EtOAc (70 mL), and washed twice with sat. aq NH_4Cl (20 mL). The combined aqueous layers were back-extracted three times with EtOAc (20 mL). The combined organic fractions were rinsed three times with brine (20 mL), dried (Na_2SO_4), and concentrated to furnish a brown oil. Purification by column chromatography (20% → 40% EtOAc/hexanes) afforded compound **11** (4.03 g, 72%) as a viscous pale yellow oil. IR: 3287, 2930, 2857, 1515. ^{1}H NMR δ: 7.01–6.90 (m, 3H), 6.77–6.70 (m, 2H), 6.34 (dt, J = 16.9, 10.4 Hz, 1H), 6.15 (d, J = 14.9 Hz, 1H), 6.02 (br s, 1H), 5.61 (d, J = 16.9 Hz, 1H), 5.53 (d, J = 10.2 Hz, 1H), 4.51 (br t, J = 6.0 Hz, 1H), 3.52–3.33 (m, 2H), 2.83 (br q, J = 6.7 Hz, 2H), 2.70 (app septet, J = 4.9 Hz, 1H), 1.94–1.63 (m, 4H), 0.86 (s, 9H), –0.02 (s, 6H). ^{13}C NMR δ: 154.6, 141.8, 135.3, 132.7, 128.8, 128.3, 127.4, 115.7, 61.1, 41.5, 39.9, 38.9, 37.0, 26.2, 18.5, –5.10, –5.14. HR-MS calcd for $C_{21}H_{36}NO_4SSi$ $[M + H]^+$: 426.2134; found: 426.2133.

***(±)-1-[1-((E)-1,3-Butadienyl)sulfonyl]-4-[1-[2-[(1,1-dimethylethyl)dimethylsilyl]-oxy]ethyl]-8-oxo-1-azaspiro[4.5]deca-6,9-diene* (12)**

The following procedure was performed with nonflame-dried glassware and unpurified solvents. A solution of sulfonamide **11** (3.01 g, 7.07 mmol, 1.0 equiv) in CH_2Cl_2 (35 mL) was added dropwise (addition funnel) over 8 min into a cooled (0 °C) solution of DIB (2.56 g, 7.79 mmol, 1.1 equiv) and TFA (600 μL, 7.79 mmol, 1.1 equiv) in CH_2Cl_2 (39 mL). The addition funnel originally containing the solution of **11** was rinsed twice with CH_2Cl_2 (2 mL), and the washes were added to the reaction mixture. The reaction was allowed to warm up and stirred for an additional 45 min at rt. Anhydrous K_2CO_3 (20 mg) was added, and the light brown suspension was concentrated to give an orange oil, which was purified by column chromatography (25% → 30% EtOAc/hexanes) to afford dienone **12** (1.57 g, 52%) as a viscous orange oil. IR: 2930, 2857, 1669, 1343. ^{1}H NMR δ: 7.00 (app dd, J = 14.9, 10.9 Hz, 1H), 6.82 (app dd, J = 9.9, 2.7 Hz, 1H), 6.67 (app dd, J = 10.6, 3.3 Hz, 1H), 6.39 (dt, J = 16.9, 10.3 Hz, 1H), 6.32–6.26 (m, 2H), 6.19 (d, J = 14.9 Hz, 1H), 5.66 (d, J = 16.9 Hz, 1H), 5.58 (d, J = 10.1 Hz, 1H), 3.65–3.52 (m, 4H), 2.52–2.30 (m, 2H), 1.84–1.67 (m, 1H), 1.41–1.29 (m, 1H),

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1.23–1.10 (m, 1H), 0.85 (s, 9H), –0.01 (s, 6H). ^{13}C NMR δ: 185.4, 151.3, 145.8, 142.8, 132.5, 130.2, 129.1, 127.9, 126.8, 66.6, 61.0, 47.9, 47.7, 31.7, 29.8, 26.0, 18.3, –5.27, –5.33. HR-MS calcd for $C_{21}H_{33}NO_4SSiNa$ [M + Na]$^+$: 446.1797; found: 446.1801.

*(3a***R****,8***S****,8a***S****,11a***R****,11b***R****)-1,3a,7,8,11a,11b-Hexahydro-8-[[2-(1,1-dimethylethyl)-dimethylsilyl]-oxy)ethyl]-6***H****,11***H****-naphtho[1,8-*cd*]pyrrolo[1,2-b]isothiazol-11-one-4,4-dioxide (***17***)***

A degassed (Ar bubbling, sonication, 15 min) solution of dienone **12** (1.57 g, 3.71 mmol, 1.0 equiv) in toluene (9.0 mL) was heated to 120 °C (oil bath temperature) for 5 h, whereupon disappearance of the starting material was observed by ^{1}H NMR. The solution was cooled to rt and diluted with more toluene (9.6 mL). Neat DBU (165 μL, 1.10 mmol, 0.3 equiv) was added; the solution was again degassed with Ar (5 min) and then heated to 58 °C (oil bath temperature) for 2 h. The mixture was cooled to rt, diluted with EtOAc (20 mL), and washed with sat. aq NH_4Cl (10 mL). The organic phase was separated and washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give crude **17** (1.53 g, contaminated with isomers as per the discussion) as a brown oil. This crude material was used without further purification. A 70% pure sample was prepared as follows: Upon completion of the IMDA reaction, the solvent was evaporated and the residue was subjected to column chromatography (20% EtOAc/hexanes). Fractions containing the anti-endo adduct **13** and some anti-exo adduct **14**, plus compound **17** arising through in situ epimerization of **13**, were combined and evaporated to afford an ~26:10:64 mixture of the three isomers, respectively. This material was dissolved in enough toluene to furnish a 0.2 mol/L solution of substrates, to which DBU (0.4 equiv) was added. The mixture was stirred at 40 °C (oil bath temperature) for 3 h, then it was cooled to room temperature, diluted with EtOAc (5 mL), rinsed with sat. aq NH_4Cl solution, washed with brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography (20% EtOAc/hexanes) afforded compound **17**, clear film, contaminated with about 15% each (^{1}H NMR) of vinyl sulfonamides **26** and **27**. These produced characteristic signals at 6.83 ppm (app q, J = 3.3 Hz) and 6.75 ppm (app q, J = 3.3 Hz). IR: 2955, 2930, 2857, 1693, ^{1}H NMR δ: 6.48 (d, J = 10.4 Hz, 1H), 6.35–6.27 (m, 1H), 6.18 (d, J = 10.4 Hz, 1H), 5.89–5.81 (m, 1H), 3.92–3.78 (m, 2H), 3.71–3.40 (m, 4H), 2.69 (dd, J = 13.7, 7.1 Hz, 1H), 2.65–2.55 (m, 1H), 2.43–2.31 (m, 1H), 2.19–2.03 (m, 2H), 1.92–1.74 (m, 1H), 1.51–1.40 (m, 2H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR δ: 198.1, 142.6, 135.3, 130.0, 115.9, 68.9, 60.8, 57.8, 48.5, 45.4, 40.2, 38.7, 32.0, 30.3, 25.97, 18.3, 24.3, –5.3. 1151. HR-MS calcd for $C_{21}H_{33}NO_4SSiNa$ [M + Na]$^+$: 446.1797; found: 446.1794.

*(3a***R****,8***S****,8a***S****,11a***R****,11b***R****)-1,3a,7,8,11a,11b-Hexahydro-8-[[2-hydroxyethyl]-6***H****,11***H****-naphtho[1,8-*cd*]pyrrolo[1,2-b]isothiazol-11-one-4,4-dioxide (***33***)***

A cold (–25 °C) solution of the crude tetracycle **17** (1.53 g, produced from 1.57 g (3.71 mmol) of dienone **12** as detailed previously) in THF (7.2 mL) was treated with TBAF (commercial 1 mol/L solution in THF; 11.0 mL, 11.0 mmol, 1.0 mol/L, 3.0 equiv). The resulting dark brown mixture was stirred at –25 °C for 4 h, then water (10 mL) was added dropwise and the mixture was warmed to rt and diluted with EtOAc (20 mL). The organic phase was separated and the aqueous layer was extracted three times with EtOAc (3 mL). The organic phases were combined, rinsed with water (5 mL) and then with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography (90% EtOAc/hexanes → EtOAc) afforded alcohol **33** (615 mg, 1.99 mmol, 53% over three steps from **12**) as a white foam. This material contained approximately 15% of the isomer emanating from compound **25**. IR: 3529, 2936, 2894, 1689, 1306, ^{1}H NMR δ: 6.47 (d, J = 10.4 Hz, 1H), 6.35–6.27 (m, 1H), 6.17 (d, J = 10.4 Hz, 1H), 5.88–5.80 (m, 1H), 3.96–3.89 (m, 1H), 3.88–3.69 (m, 2H), 3.66–3.38 (m, 3H), 2.68 (dd, J = 13.6, 7.1 Hz, 1H), 2.65–2.54 (m, 1H), 2.46–2.34 (m, 1H), 2.20–2.04 (m, 2H), 1.91–1.74 (m, 1H), 1.68 (br s, 1H), 1.60–1.35 (m, 2H). ^{13}C NMR δ: 198.1, 142.6, 135.3, 130.0, 115.7, 68.9, 60.7, 57.8, 48.5, 45.6, 40.2, 38.7, 31.6, 30.0, 24.2. 1148. HR-MS calcd for $C_{15}H_{19}NO_4SNa$ [M + Na]$^+$: 332.0932; found: 332.0935.

*(3a***R****,8***S****,8a***S****,11a***R****,11b***R****)-1,3a,7,8,11a,11b-Hexahydro-8-[[2-iodoethyl]-6***H****,11***H****-naphtho[1,8-*cd*]pyrrolo[1,2-b]isothiazol-11-one-4,4-dioxide (***34***)***

Solid I_2 (506 mg, 1.99 mmol, 2.3 equiv) was added to a chilled (0 °C) solution of alcohol **33** (265 mg, 867 μmol, 1.0 equiv), PPh_3 (459 mg, 1.75 mmol, 2.0 equiv), and imidazole (148 mg, 2.17 mmol, 2.5 equiv) in THF (2.8 mL). After 5 min, the reaction flask was taken out of the ice bath and the solution was stirred at rt for 2 h. The mixture was diluted with EtOAc (10 mL) and rinsed twice with 10% aq $Na_2S_2O_3$ solution (5 mL). The combined aqueous phases were back-extracted once with ethyl acetate (3 mL). The combined organic phases were rinsed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (30% → 40% EtOAc/hexanes) afforded the title compound (318 mg, 87%) as a yellow solid; mp 189–192 °C (dec.). This material contained approximately 15% of the isomer emanating from compound **25**. IR: 2934, 2898, 1689, 1306, 1137. ^{1}H NMR δ: 6.45 (d, J = 10.4 Hz, 1H), 6.36–6.28 (m, 1H), 6.17 (d, J = 10.4 Hz, 1H), 5.89–5.82 (m, 1H), 3.98–3.81 (m, 2H), 3.58–3.38 (m, 2H), 3.35–3.26 (m, 1H), 3.09–2.98 (m, 1H), 2.66–2.55 (m, 2H), 2.45–2.34 (m, 1H), 2.20–2.02 (m, 2H), 1.84–1.61 (m, 3H). ^{13}C NMR δ: 197.7, 142.1, 135.3, 130.2, 115.6, 68.5, 57.7, 49.2, 48.1, 40.1, 38.6, 32.6, 29.0, 24.2, 4.0. HR-MS calcd for $C_{15}H_{19}INO_3S$ [M + H]$^+$: 420.0130; found: 420.0130.

*3-((3a***R****,3a^1***R****,8***R****,8a***S****,11a***R****)-1,3a,3a^1,6,7,8,11,11a-Octahydronaphtho[1,8-*cd*]pyrrolo[1,2-b]isothiazol-8-yl)-11-oxo-propanenitrile-4,4-dioxide (***31***)***

Solid Et_4N^+ $^-$CN (132 mg, 0.794 mmol, 1.1 equiv) was added in one portion to a chilled (0 °C) solution of iodide **34** (300 mg, 0.716 mmol, 1.0 equiv) in MeCN (2.4 mL). The reaction flask was taken out of the ice bath and stirred at rt for 30 min. The suspension was diluted with EtOAc (5 mL) and rinsed twice with 10% $Na_2S_2O_3$ aqueous solution (2 mL). The aqueous fractions were combined and extracted three times with EtOAc (1 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (60% → 65% EtOAc/hexanes) afforded **31** (200 mg, 88%) as a white solid; mp 183–187 °C (dec.). This material contained approximately 15% of the isomer emanating from compound **25**. IR: 2936, 2248, 1690, 1307, 1148. ^{1}H NMR δ: 6.45 (d, J =

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10.5 Hz, 1H), 6.37–6.28 (m, 1H), 6.21 (d, J = 10.5 Hz, 1H), 5.89–5.81 (m, 1H), 3.98–3.83 (m, 2H), 3.61–3.51 (m, 1H), 3.50–3.39 (m, 1H), 2.68–2.31 (m, 5H), 2.20–1.98 (m, 2H), 1.93–1.80 (m, 1H), 1.76–1.62 (m, 1H), 1.61–1.46 (m, 1H). ^{13}C NMR δ: 197.6, 141.5, 135.4, 130.6, 118.5, 115.5, 68.6, 57.7, 48.3, 47.9, 40.2, 39.0, 29.3, 25.1, 24.2, 16.5. HR-MS calcd for $C_{16}H_{18}N_2O_3SNa$ [M + Na]$^+$: 341.0936; found: 341.0949.

***3-((3aR*,3a¹R*,8R*,8aS*,11aR*)-1,3a,3a¹,6,7,8,11,11a-Octahydronaphtho[1,8-cd]pyrrolo[1,2-b]isothiazol-8-yl)-11-oxo-propanal-4,4-dioxide* (35)**

Commercial DIBAL in hexanes (1 mol/L, 0.25 mL, 0.25 mmol, 3.0 equiv) was added dropwise to a cold (–78 °C) solution of **31** (26 mg, 0.082 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL). The mixture was stirred at –78 °C for 5 h, and then it was quenched by careful addition of MeOH (0.1 mL). The reaction was taken out of the cold bath, diluted with EtOAc (2 mL), and treated with sat. aq Rochelle's salt solution (2 mL). The resulting biphasic mixture was vigorously stirred overnight at rt. The organic phase was separated and the aqueous layer was extracted three times with EtOAc (1 mL). The combined organic phases were rinsed with brine, dried (Na_2SO_4), and concentrated. The crude product, a mixture of diastereomers of the secondary alcohol, was directly dissolved in CH_2Cl_2 (0.35 mL) and Dess–Martin periodinane (52 mg, 0.12 mmol, 1.5 equiv) was added in one portion. The white suspension was allowed to stir at rt for 2 h. The reaction was diluted with EtOAc (2 mL) and rinsed twice with 1:1 (v/v) 10% aq $Na_2S_2O_3$ / sat. aq $NaHCO_3$ (1 mL). The combined aqueous layers were back-extracted three times with EtOAc (1 mL). The combined extracts were rinsed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (75% → 80% EtOAc/hexanes) gave **35** as a clear film (7 mg, 27%). This material contained approximately 15% of the isomer emanating from compound **25**. IR: 2927, 1719, 1690, 1307, 1148. ^{1}H NMR δ: 9.76 (br s, 1H), 6.47 (d, J = 10.5 Hz, 1H), 6.36–6.28 (m, 1H), 6.20 (d, J = 10.5 Hz, 1H), 5.89–5.81 (m, 1H), 3.93–3.76 (m, 2H), 3.56–3.37 (m, 2H), 2.74 (dd, J = 13.6, 7.1 Hz, 1H), 2.68–2.48 (m, 3H), 2.35–2.25 (m 1H), 2.21–2.07 (m, 1H), 1.93–1.64 (m, 3H), 1.44–1.29 (m, 1H). ^{13}C NMR δ: 200.7, 197.8, 142.1, 135.3, 130.3, 115.6, 69.0, 57.8, 48.2, 48.0, 42.0, 40.2, 38.6, 29.7, 24.2, 21.1. HR-MS calcd for $C_{17}H_{24}NO_5S$ [M + MeOH + H]$^+$: 354.1375; found: 354.1387.

***Compound* 36**

Pyrrolidine (49 μL, 593 μmol, 10 equiv) was added to solution of aldehyde **35** (19 mg, 59 μmol, 1.0 equiv) in THF (0.6 mL) at rt. The mixture was heated to 30 °C (oil bath temperature) and stirred for 14 h, then it was quenched with 1 mol/L HCl (1 mL), stirred for 30 min at rt, and then diluted with EtOAc (3 mL). The organic phase was separated and the aqueous layer extracted five times with EtOAc (1 mL). The combined extracts were rinsed with brine (2 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (70% EtOAc/hexanes) afforded pentacyclic substance **36** (8 mg, 42%, clear film) as a 1:1 mixture of α- and β-aldehyde diastereomers. This material was free of isomeric products emanating from compound **25**. IR: 2936, 1716, 1151. ^{1}H NMR δ: 9.79 (s, 1H) and 9.70 (s, 1H), 6.31–6.22 (m, 2H), 5.88–5.78 (m, 2H), 4.15–4.04 (m, 1H), 3.86–3.76 (m, 1H), 3.58–3.08 (m, 9H), 2.75 (d, J = 5.4 Hz, 1H), 2.69 (d, J = 5.4 Hz, 1H), 2.60–2.28 (m, 7H), 2.27–2.17 (m, 3H), 2.14–2.00 (m, 3H), 1.98–1.78 (m, 4H), 1.66–1.55 (m, 2H). ^{13}C NMR δ: 209.6, 209.0, 200.7, 199.7, 134.5, 134.4, 115.7, 115.5, 79.7, 79.2, 60.54, 60.51, 56.0, 55.2, 52.1, 52.0, 51.7, 50.2, 44.52, 44.48, 43.5, 42.6, 41.7, 41.6, 41.3, 37.3, 32.9, 30.3, 28.7, 27.5, 24.4 (two signals). HR-MS calcd for $C_{16}H_{20}NO_4S$ [M + H]$^+$: 322.1113; found: 322.1109.

Supplementary data

Supplementary data (experimental procedures for the preparation of compound **24** and characterization data) are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0340.

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