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Concise synthesis of azacycloundecenes using ring-closing metathesis (RCM)

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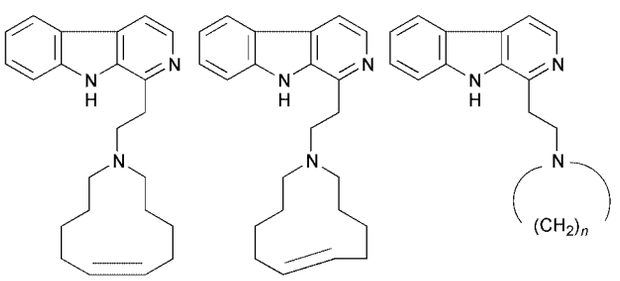
Azacycloundecenes, which are key intermediates in the synthesis of derivatives of the marine alkaloid manzamine C, are conveniently prepared using ring-closing olefin metathesis (RCM).

Introduction

Manzamines are a class of cytotoxic β-carboline alkaloids that were isolated from Okinawan marine sponges by Higa and co-workers. Manzamine C **1** is the simplest congener and bears an

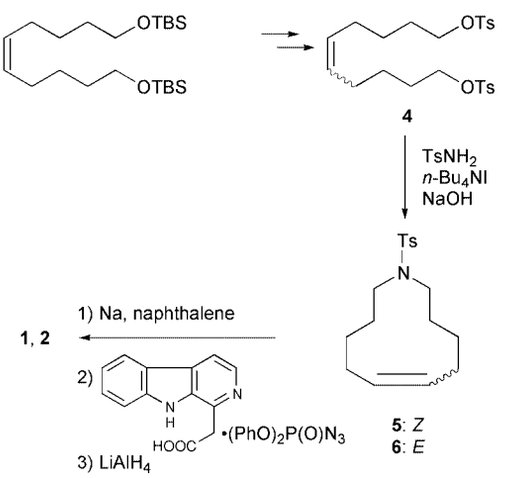


unprecedented azacycloundecene ring.[1] The total synthesis of **1** was first achieved by one of us[2] and afterwards by Gerlach's group[3a] and by Langlois' group[3b] using their own original methods. In the original synthesis of **1** and *trans*-(*E*)-manzamine C **2**, (*Z*)- and (*E*)-azacycloundecenes were key intermediates, and were prepared by conventional methods. Our colleagues have also successfully developed an efficient synthetic route to the saturated congener **3** in order to determine possible structure–activity relationships.[4] Manzamine C **1**, despite its rather simple structure, shows some of the cytotoxic activity found in manzamine A. Therefore the synthesis of **1** and related analogues is attractive from the perspective of structure–activity relationships.

Recently, the chemistry of carbene complexes of transition metals has been extensively studied. In particular the ring-closing olefin metathesis (RCM) developed by Grubbs' group has become a useful and novel method for constructing cyclic alkenes.[5] In this paper, a convenient method for preparing azacycloundecenes using RCM is described.

Results and discussion

The formation of 11-membered rings by RCM is distinctly unusual.[5b] Recently Gesson and co-workers successfully used RCM in the synthesis of 11-membered lactones from carbohydrate derivatives.[6] As shown in Scheme 1, azacycloundecene compounds (**5** or **6**), which are key intermediates in our syntheses of **1** and **2**, were prepared by cyclization of the ditosyl compound **4** derived from the corresponding alkyne. To investigate an alternative, convenient method for the synthesis of **5** or



Scheme 1

6, we studied the RCM of **7**, which can be readily obtained in 83% yield by reaction of toluene-*p*-sulfonamide with 6-bromohex-1-ene. The results are shown in Table 1.

RCM with 10 mol% of the Grubbs catalyst **8** in CH_2Cl_2 (0.020 M) converted **7** to a single isomer of a cyclized product (16% yield), which was identified as the *E* isomer **6** by comparison with an authentic sample prepared previously,[2] together with dimeric products. On the other hand, the same reaction of **7** in a more dilute solution (0.002 M) gave two cyclized products, **6** (major) and the *Z* isomer **5** (minor) (run 2), which were readily separated by column chromatography. The yield was increased to 74% when the reactants were heated at 50 °C (run 3).

We were interested in the biological activity of an oxygen-functionalized analogue **9**, which was expected to be more soluble in water. Metathesis substrate **11** was prepared by diallylation of the corresponding diol **12**, which was obtained in

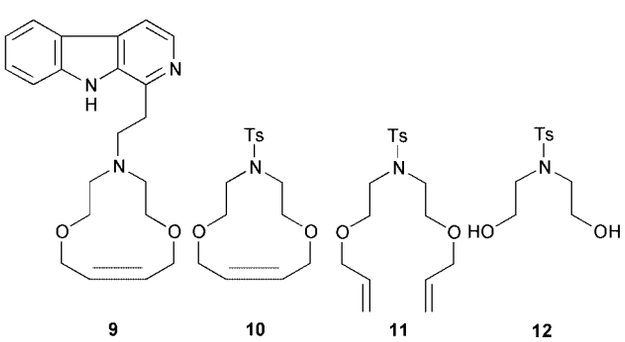


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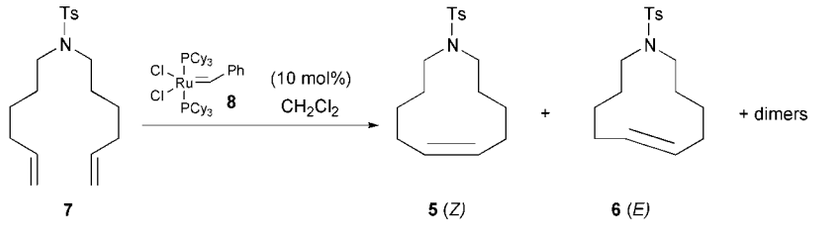
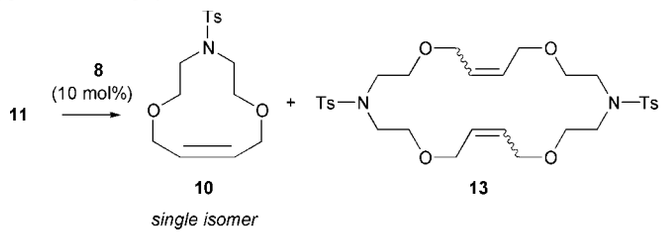
Table 1 RCM: construction of cycloundecenes



Run	Substrate concn. (M)	Temp. (*T*/°C)	Reaction time (*t*/h)	**5** (%)	**6** (%)
1	0.02	rt	5.5	0	16
2	0.002	rt	5.5	4	50
3	0.002	50	2.5	12	62

Table 2 RCM: construction of oxygen-containing cycloundecenes

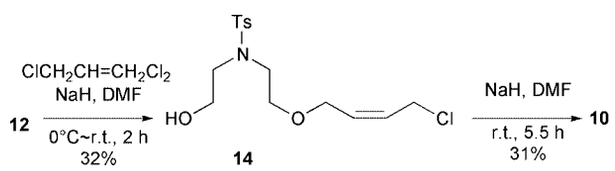


Run	Solvent	Substrate concn. (M)	Temp. (*T*/°C)	Reaction time	**10** (%)	**13** (%)
1	Benzene	0.02	rt	4 d	11	62
2	CH_2Cl_2	0.02	rt	15 h	25	67
3	CH_2Cl_2	0.002	rt	15 h	53	32
4	CH_2Cl_2	0.002	50	15 h	49	41

66% yield from the reaction of a protected bromoethanol with toluene-*p*-sulfonamide (3 steps).

Reaction of **11** in 0.02 M solution of CH_2Cl_2 or benzene using 10 mol% of **8** gave dimeric compound **13** (62–67%) and the (*Z*)-cycloundecene **10** (11–25%) (Table 2, runs 1 and 2).

Under more dilute conditions, in 0.002 M solution, **10** became the main product (53%, run 3). The yield of **10** did not increase when the reaction mixture was heated. The structure of **10** was determined by X-ray analysis and comparison of the spectral data with those of an authentic specimen prepared from stepwise etherification of diol **12** *via* the monoether **14** (Scheme 2). In contrast to **7**, the same reaction of **11** gave only



Scheme 2

Z isomer **10**, probably for conformational reasons. Thus, it is clear that RCM is an effective method for preparing oxygen-containing (*Z*)-undecene intermediates for manzamine C analogues, compared with the conventional method, and this will now be extended to the synthesis of marine alkaloids.

In summary, we have found that RCM easily gives key intermediates for the synthesis of manzamine C analogues. These results suggest that even small structural variations can significantly alter the stereochemical outcome. Further studies in which the present results are extended to the synthesis of azacycles including stereoselective RCM are currently in progress.

Experimental

All mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR absorption spectra were recorded using a JASCO FTIR-230 spectrometer. ^{1}H NMR (and ^{13}C NMR) spectra were recorded for samples in $CDCl_3$ unless otherwise noted, at 400 MHz (JEOL-400α), with TMS as internal standard. E. Merck silica gel 60 was used for column chromatography, and E. Merck precoated TLC plates, silica gel F_{254}, were used for preparative TLC. The organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4. $Cl_2(PCy_3)_2Ru$=CHPh **8** is commercially available.

N,*N*-Di(hex-5-enyl)toluene-*p*-sulfonamide 7

To a 100 mL flask were added 6-bromohex-1-ene (1.63 g, 10.0 mmol), benzene (34.0 mL), water (2.00 mL), *n*-Bu_4NI (1.85 g, 5.00 mmol, 0.500 equiv.), toluene-*p*-sulfonamide (1.03 g, 0.600 mmol, 0.600 equiv.) and NaOH (800 mg, 20.0 mmol, 2.00 equiv.), and the mixture was refluxed for 2.5 h. The reaction mixture was extracted with AcOEt, and the extract was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude residue was subjected to column chromatography (*n*-hexane–AcOEt 3:1) to yield compound **7** (1.45 g, 83%) as a yellow oil; ν_{max}(neat)/cm^{-1} 3074, 2933, 1640, 1340, 1158, 910 and 723; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.67 (2H, d, *J* 8.1 Hz), 7.28 (2H, d, *J* 8.1 Hz), 5.80–5.70 (2H, m), 5.01–4.92 (4H, m), 3.09 (4H, t, *J* 7.5 Hz), 2.41 (3H, s), 2.03 (4H, td, *J* 7.2, 7.1 Hz), 1.56–1.49 (4H, m), 1.39–1.32 (4H, m); δ_C(100 MHz; $CDCl_3$; Me_4Si) 142.87, 138.27, 137.08, 129.51, 127.06, 114.73, 48.01, 33.18, 27.99, 25.87, 21.40; *m*/*z* (FAB) 336.2001 ($M^+ + H$. $C_{19}H_{30}NO_2S$ requires *m*/*z* 336.1997).

N,*N*-Bis(2-hydroxyethyl)toluene-*p*-sulfonamide 12

To a 200 mL flask containing 3,4-dihydro-2*H*-pyran (14.8 g,

180 mmol, 1.10 equiv.), was added *p*-TsOH (10.0 mg). The mixture was stirred at ambient temperature for 10 min. 2-Bromoethanol (20.0 g, 160 mmol) was added dropwise over a period of 25 min, and the mixture was stirred for 10 min. The reaction was quenched by $NaHCO_3$ (1.00 g), and the mixture was stirred for 50 min at rt and filtered. The filtrate was evaporated under reduced pressure and the obtained residue was subjected to column chromatography (*n*-hexane–AcOEt 30 : 1 ~ 10 : 1) to yield 2-(2-bromoethoxy)tetrahydropyran (29.1 g, 87%) as a colorless oil.

To a 500 mL flask were added 2-(2-bromoethoxy)tetrahydropyran (14.7 g, 70.3 mmol), benzene (240 mL), water (12.0 mL), *n*-Bu_4NI (12.9 g, 34.9 mmol, 0.500 equiv.), toluene-*p*-sulfonamide (7.20 g, 42.1 mmol, 0.600 equiv.) and NaOH (5.60 g, 140 mmol, 2.00 equiv.), and the mixture was refluxed for 3 h. More toluene-*p*-sulfonamide (2.00 g, 11.7 mmol, 0.170 equiv.) was added, and the mixture was refluxed for 3 h. The product was extracted with AcOEt, and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude residue was subjected to column chromatography (*n*-hexane–AcOEt 3 : 1) to yield *N*,*N*-bis[2-(tetrahydropyran-2-yloxy)ethyl]toluene-*p*-sulfonamide (13.8 g, 93%) as a yellow oil.

To a stirred solution of *N*,*N*-bis[2-(tetrahydropyran-2-yloxy)ethyl]toluene-*p*-sulfonamide (13.8 g, 32.3 mmol) in MeOH (450 mL) was added Amberlist-15 (2.20 g), and the mixture was stirred at rt for 12 h. After the resin was removed by filtration, the solvent was evaporated under reduced pressure to give a residue, which was purified by crystallization from benzene to give the title diol **12** (6.89 g, 82%) as colorless needles.

2-(2-Bromoethoxy)tetrahydropyran. ν_{max}(neat)/cm^{-1} 2950, 1120 and 1030; δ_H(400 MHz; $CDCl_3$; Me_4Si) 4.68 (1H, t, *J* 3.6 Hz), 4.02 (1H, td, *J* 12.0, 5.6 Hz), 3.89 (1H, ddd, *J* 11.4, 8.2, 3.3 Hz), 3.77 (1H, td, *J* 12.2, 5.6 Hz), 3.48–3.56 (3H, m), 1.52–1.88 (6H, m).

***N*,*N*-Bis[2-(tetrahydropyran-2-yloxy)ethyl]toluene-*p*-sulfonamide.** ν_{max}(neat)/cm^{-1} 2950, 1350, 1160, 1040 and 740; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.73 (2H, d, *J* 8.3 Hz), 7.28 (2H, d, *J* 8.0 Hz), 4.53 (2H, br s), 3.76–3.89 (4H, m), 3.40–3.59 (8H, m), 2.41 (3H, s), 1.49–1.78 (12H, m); δ_C(100 MHz; $CDCl_3$; Me_4Si) 143.10, 137.16, 129.55, 127.20, 98.97, 66.30, 62.22, 48.68, 30.48, 25.34, 24.45, 19.39; *m*/*z* (FAB) 428 (M^+ + H), 344 (M^+ + H − THP), 260 (M^+ + H − 2THP).

Compound 12. Mp 104.0–104.5 °C (from benzene); ν_{max}(KBr)/cm^{-1} 3230, 1330, 1155, 710 and 690; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.70 (2H, d, *J* 8.3 Hz), 7.33 (2H, d, *J* 8.5 Hz), 4.11 (2H, br s), 3.85 (4H, br s), 3.26 (4H, t, *J* 4.9 Hz), 2.43 (3H, s); δ_C(100 MHz; $CDCl_3$; Me_4Si) 143.69, 135.12, 129.80, 127.23, 62.13, 52.92, 21.44; *m*/*z* (FAB) 260.0961 (M^+ + H. $C_{11}H_{18}NO_4S$ requires *m*/*z*, 260.0957) (Found: C, 51.18; H, 6.57; N, 5.37. Calc. for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40%).

Preparation of *N*,*N*-bis(2-allyloxyethyl)toluene-*p*-sulfonamide 11

To a stirred solution of diol **12** (1.04 g, 4.00 mmol) in DMF (40.0 mL) was added NaH (60% oil dispersion; 480 mg, 12.0 mmol, 3.00 equiv.) at 0 °C, and the mixture was stirred for 30 min. Allyl bromide (1.04 mL, 12.0 mmol, 3.00 equiv.) was then added, and the mixture was stirred for 1 h. The reaction was quenched by water, and the product was extracted with AcOEt. Combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (*n*-hexane–AcOEt 4 : 1 ~ 1 : 1) to yield title compound **11** (846 mg, 63%) as a colorless oil; ν_{max}(KBr)/cm^{-1} 2926, 2863, 1343, 1157, 737 and 715; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.72 (2H, d, *J* 8.3 Hz), 7.28 (2H, d, *J* 8.6 Hz), 5.84 (2H, ddt, *J* 17.3, 10.5, 5.4 Hz), 5.23 (2H, dtd, *J* 17.3, 1.7, 1.6 Hz), 5.16 (2H, dtd, *J* 10.5, 1.5, 1.4 Hz), 3.93 (4H, ddd, *J* 5.7, 1.5, 1.5 Hz), 3.59 (4H, t, *J* 6.0 Hz), 3.40 (4H, t, *J* 6.1 Hz), 2.42 (3H, s); δ_C(100 MHz; $CDCl_3$; Me_4Si) 143.05, 136.83, 134.35, 129.46, 127.05, 116.82, 71.81, 69.00, 48.74, 21.32; *m*/*z* (FAB) 340.1580 (M^+ + H. $C_{17}H_{26}NO_4S$ requires *m*/*z*, 340.1583).

General procedure for RCM

RCM of 7. To a stirred solution of diene **7** (70.3 mg, 0.200 mmol) in CH_2Cl_2 (100 mL) was added catalyst **8** (16.4 mg, 0.0200 mmol). The solution was degassed three times by the freeze–pump–thaw (FPT) method and the reaction mixture was stirred at 50 °C for 2.5 h. The solvent was removed under reduced pressure to give a residue, which was purified by silica gel column chromatography (*n*-hexane–AcOEt 3 : 1). Azacycloundecenes **5** (7.4 mg, 12%) and **6** (38.3 mg, 62%) were isolated as a white powder and white crystals, respectively.

RCM of 11. To a stirred solution of **11** (67.9 mg, 0.200 mmol) in CH_2Cl_2 (100 mL) was added **8** (16.4 mg, 0.0200 mmol). The solution was degassed three times (FPT) and the reaction mixture was stirred at rt for 15 h. The solvent was removed under reduced pressure to give a residue, which was purified by silica gel column chromatography (*n*-hexane–AcOEt 2 : 1). Heterocycles **10** (32.9 mg, 53%) and **13** (20.1 mg, 32%) were isolated, both as colorless needles.

Compound 10. Mp 87.0–89.0 °C (from AcOEt); ν_{max}(KBr)/cm^{-1} 2960, 2941, 2912, 2866, 1335, 1165 and 742; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.69 (2H, d, *J* 8.2 Hz), 7.31 (2H, d, *J* 8.2 Hz), 5.76 (2H, m), 4.28 (4H, dd, *J* 3.7, 1.2 Hz), 3.79 (4H, t, *J* 4.7 Hz), 3.27 (4H, t, *J* 4.7 Hz), 2.43 (3H, s); δ_C(100 MHz; $CDCl_3$; Me_4Si) 143.36, 135.45, 129.69, 129.67, 127.30, 68.82, 66.86, 51.31, 21.48; *m*/*z* (FAB) 312.1263 (M^+ + H. $C_{15}H_{22}NO_4S$ requires *m*/*z*, 312.1270) (Found: C, 57.69; H, 6.62; N, 4.50. Calc. for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50%).

*X-Ray crystal structure analysis of compound **10**.*—Crystal dimensions 0.45 × 0.36 × 0.45 mm, triclinic, *P*1(#2), *a* = 9.613(10), *b* = 9.77(1), *c* = 9.05(1) Å, *α* = 95.92(7), *β* = 102.94(6), *γ* = 103.18(5)°, *V* = 795(1) Å^3, *Z* = 2, D_{calc} = 1.229 g cm^{-3}, *T* = 298 K, *F*(000) = 332. Rigaku RAXIS-II Imaging Plate diffractometer, *λ*(Mo-K*α*) = 0.710 70 Å, *μ* = 2.18 cm^{-1}. The final refinement of F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2) = 0.083$ for 2537 reflections with $R(F) = 0.067$ for 2377 reflections obeying $F_0 > 3.0\ \sigma(F_0)$ and 191 parameters.

*Compound **13**.*—Mp 147.5–148.3 °C (from AcOEt); ν_{max}(KBr)/cm^{-1} 2931, 2866, 1344, 1165 and 737; δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.69 (4H, d, *J* 8.2 Hz), 7.29 (4H, d, *J* 8.2 Hz), 5.76–5.97 (4H, m), 3.94 (8H, dd, *J* 2.5, 1.5 Hz), 3.63 (8H, t, *J* 5.9 Hz), 3.36 (8H, t, *J* 5.9 Hz), 2.42 (6H, s); δ_C(100 MHz; $CDCl_3$; Me_4Si) 143.29, 136.30, 129.67, 128.65, 127.17, 70.81, 69.96, 49.44, 21.48; *m*/*z* (FAB) 623.2461 (M^+ + H. $C_{30}H_{43}N_2O_8S_2$ requires *m*/*z*, 623.2461) (Found: C, 57.56; H, 6.67; N, 4.40. Calc. for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50%).

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