ChemComm

Synthesis of fused bicyclic medium-ring lactones *via* Claisen rearrangement

Jonathan W. Burton,*[a] Paul T. O'Sullivan,[a] Edward A. Anderson,[a] Ian Collins[b] and Andrew B. Holmes*[a]

[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: abh1@cam.ac.uk; jwb1004@cam.ac.uk*

[b] *Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, UK CM20 2QR*

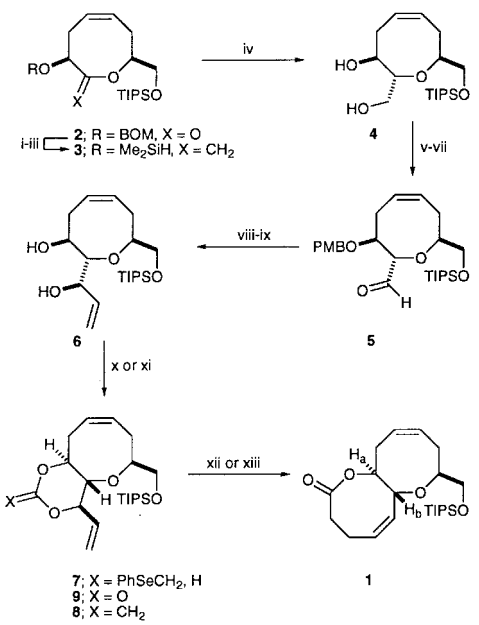
Received (in Cambridge, UK) 6th January 2000, Accepted 4th February 2000

Fused bicyclic medium-ring lactones, carrying identical ring-fusion to that in the polyether toxins, are prepared by a Claisen rearrangement sequence.

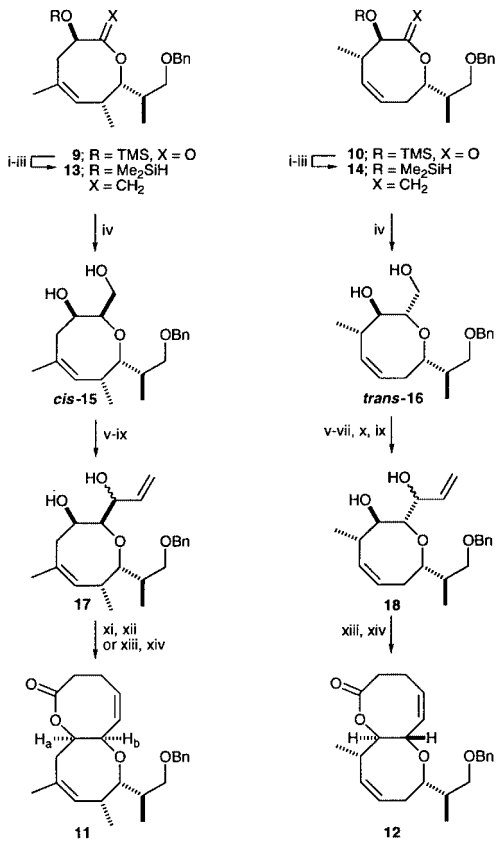
The polyether neurotoxins have attracted enormous synthetic interest as a result of their unusual molecular architecture and biological activity.[1] Most recently Nicolaou *et al.* have described the total synthesis of brevetoxin A,[2,3] and there have been many contributions from others active in this field.[4] Here, we report the use of the Claisen rearrangement to prepare fused bicyclic medium-ring lactones having the precise structural features present in the medium-ring fused polyether segments of brevetoxin B and ciguatoxin.

Our approach to fused medium-ring lactones follows the methodology previously developed for the synthesis of obtusenyne[5,6] and (+)-laurencin.[7] Transformation of a 1,3-diol into a vinyl-substituted ketene acetal by selenoxide elimination or carbonate methylenation (see preceding Communication) provides the desired medium-ring fused bicyclic lactone after Claisen rearrangement.

Scheme 1† summarises the construction of the bicyclic lactone **1**. Methylenation (72%) of the monocyclic lactone **2**,‡ BOM deprotection (94%) and silylation with $(Me_2SiH)_2NH$ (100%) provided the silane **3**. Rhodium catalysed intra-



Scheme 1 Synthesis of the bicyclic lactone **1**. *Reagents and conditions*: i, Cp_2TiMe_2, toluene, reflux, 40 min, 72%; ii, LiDBB (excess), THF, −78 °C, 3 min, 94%; iii, 1,1,3,3-tetramethyldisilazane, NH_4Cl (cat.), 60 °C, 18 h, 100%; iv, (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate (3 mol%), THF, 60 °C, 18 h, then $Na_2EDTA{\cdot}2H_2O$, 1 h, then 15% aqueous KOH, 30% aqueous H_2O_2, THF and methanol, 1 h, then $Na_2S_2O_3$, 86%; v, *p*-methoxybenzaldehyde, PPTS (cat.), benzene, Dean–Stark, 12 h, 85%; vi, DIBAL-H, toluene, CH_2Cl_2, $-78 \rightarrow -50 \rightarrow -30$ °C, 2.5 h, 80%; vii, IBX, Me_2SO, room temp., 18 h; viii, $CeCl_3$, THF, 18 h, then vinylmagnesium bromide, THF, −78 °C, 2 h, then **5**, −78 °C, 1.5 h, 74%; ix, CH_2Cl_2–TFA (5:1), −20 °C, 10 min, 90%; x, $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 2 h, 94%, xi, triphosgene, pyridine, Et_3N, CH_2Cl_2, 4 Å molecular sieves, −78 °C → room temp., 89%; xii, $NaIO_4$, $NaHCO_3$, CH_2Cl_2, methanol, water, 2 h, then DBU, toluene, reflux, 18 h, 90%; xiii, Cp_2TiMe_2, toluene, reflux, 1.5 h, 63%. BOM = benzyloxymethyl; IBX = *o*-iodoxybenzoic acid; LiDBB = lithium di-*tert*-butylbiphenylide.



Scheme 2 Synthesis of the bicyclic lactones **11** and **12**. *Reagents and conditions*: i, Cp_2TiMe_2, toluene, reflux; ii, K_2CO_3, methanol, 85% from **9**, 76% from **10**; iii, 1,1,3,3-tetramethyldisilazane, NH_4Cl (cat.), 60 °C, 18 h, 99% for **13**, 98% for **14**; iv, (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate (3 mol%), THF, 60 °C, 18 h, then $Na_2EDTA{\cdot}2H_2O$, 1 h, then 15% aqueous KOH, 30% aqueous H_2O_2, THF and methanol, 1 h, then $Na_2S_2O_3$, 61% for *cis*-**15**, 57% for *trans*-**16**; v, *p*-methoxybenzaldehyde, PPTS (cat.), benzene, Dean–Stark; vi, DIBAL-H, toluene, CH_2Cl_2; vii, IBX, Me_2SO, room temp., 18 h; viii, $CeCl_3$, THF, 18 h, then vinylmagnesium bromide, THF, −78 °C, 2 h, add aldehyde, −78 °C, 1.5 h; ix, CH_2Cl_2–TFA (5:1), −20 °C, 10 min, 58% from **15**, 24% from **16**; x, vinyl iodide, $CrCl_2$ 1% $NiCl_2$, Me_2SO, 72 h; xi, $PhSeCH_2CH(OEt)_2$, PPTS, toluene; xii, $NaIO_4$, $NaHCO_3$, CH_2Cl_2, methanol, water, 2 h, then DBU, toluene, reflux, 18 h, 58% from **17**; xiii, triphosgene, pyridine, Et_3N, CH_2Cl_2, 4 Å molecular sieves, −78 °C → room temp.; xiv, Cp_2TiMe_2, toluene, reflux, 1.5 h, 38% from **17**, 43% from **18**. IBX = *o*-iodoxybenzoic acid.

DOI: 10.1039/b000303o

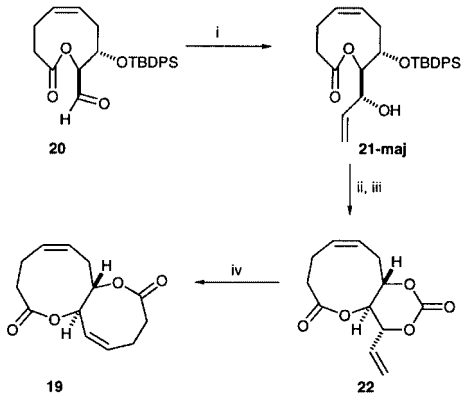
molecular hydrosilation[5,7] followed by oxidation yielded the diol **4** (86%) as a single diastereomer (^{1}H NMR). *p*-Methoxybenzylidene acetal formation (85%), reduction with DIBAL-H (79%) and IBX oxidation[8] furnished the labile aldehyde **5**. Exposure of **5** to vinylmagnesium bromide in the presence of cerium(III) chloride, according to the procedure of Imamoto,[9] provided the corresponding allylic alcohols (85%, 5:1 mixture of diastereomers, Felkin control). The major diastereomer was deprotected with TFA to furnish the diol **6** (90%). Heating a solution of **6** and phenylselenoacetaldehyde diethyl acetal in acidic toluene provided the selenides **7** (94%, mixture of diastereomers) which were oxidised to the corresponding selenoxides. Pyrolysis of the selenoxides in toluene at reflux yielded the desired *trans*-fused bicyclic lactone **1** (90%, single diastereomer, $J_{a,b}$ 9.7 Hz) presumably *via* the intermediate ketene acetal **8**. Alternatively the diol **6** could be converted into the corresponding carbonate **9** (89%), which on heating with dimethyltitanocene provided **1** (63%). Thus the conversion of a medium-ring lactone into the corresponding *trans*-fused bicyclic lactone has been achieved in 11 synthetic steps and 25% overall yield.

In a similar manner the lactones **9**‡ and **10**‡ were converted into the corresponding bicyclic lactones **11** and **12** (Scheme 2†). The silanes **13** and **14** were synthesised from the lactones **9** and **10** by an analogous route to that depicted in Scheme 1. Rhodium catalysed intramolecular hydrosilation converted **13** into the diols **15** (61% combined yield, 6:1 mixture of *cis*:*trans* diastereomers, major diastereomer shown) after oxidative work-up. Similarly exposure of the silane **14** to the hydrosilation conditions provided the diols **16** after work-up (57% combined yield, 1.33:1, mixture of *trans*:*cis* diastereomers, major diastereomer shown). Conversion of the major diastereomers *cis*-**15** and *trans*-**16** into the corresponding allylic alcohols **17** and **18** proceeded without incident. The *cis*-fused bicyclic lactone **11** ($J_{a,b}$ 2.4 Hz) was accessed from the diols **17** *via* both the selenoacetal route (58% for three steps) and the carbonate route (38% for two steps) thus demonstrating the versatility of this method for the synthesis of bicyclic lactones. It also proved possible to convert the diols **18** into the *trans*-fused bicyclic lactone **12** *via* initial conversion to the corresponding carbonates (90%) followed by heating in the presence of dimethyltitanocene (48%).

The synthesis of the 8,9-*trans*-fused bicyclic lactone **19** was achieved *via* elaboration of the known nine-membered lactone-aldehyde **20** (Scheme 3†).[10] Treatment of **20** with vinyl iodide in the presence of chromium(II) chloride in Me_2SO[11] provided the allylic alcohols **21** (59%, 2:1 mixture of diastereomers, Felkin control, major diastereomer shown). The allylic alcohol **21-maj** was deprotected (50–69%) and converted into the crystalline carbonate **22** {78%, mp 126–127 °C (from hexane)}. Treatment of **22** with dimethyltitanocene in toluene at reflux provided the crystalline *trans*-fused bicyclic lactone **19**§ [25% unoptimised, mp 109–111 °C (from hexane)] and recovered starting material (75%).

In summary, we have shown that the Claisen rearrangement and hydrosilation methodology, developed for the synthesis of medium-ring oxygen-containing heterocycles, can readily be extended to the synthesis of *cis*- or *trans*-fused bicyclic medium-ring lactones which form the basis for the synthesis of members of the polyether toxin family.

We thank the EPSRC for financial support and provision of the Swansea MS service, Merck, Sharp and Dohme for a CASE award (to E. A. A.), the University of Cambridge (Robert Gardiner Memorial Scholarship), the Cambridge European Trust (awards to P. T. O'S) and Corpus Christi College, Cambridge (Research Fellowship, J. W. B.).



Scheme 3 Synthesis of the bicyclic lactone **19**. *Reagents and conditions*: i, vinyl iodide, $CrCl_2$ 1% $NiCl_2$, Me_2SO, 18 h, 59%; ii, HF·pyridine, pyridine, THF, 50–69%; iii, triphosgene, pyridine, Et_3N, CH_2Cl_2, 4 Å molecular sieves, −78 °C → room temp., 78%; iv, Cp_2TiMe_2, toluene, reflux, 1.5 h, 25%.

Notes and references

† All new compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data.

‡ The synthesis of the lactones **2**, **9** and **10** will be reported in a separate paper.

§ *Selected data* for compound **19**: white crystalline solid; mp 109–111 °C (from hexane); R_f 0.6 (diethyl ether–hexane, 1:1); $[\alpha]_D^{16}$ −26.6 (*c* 0.165 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2947, 1744 (CO), 1737 (CO), 1340, 1149 and 1068; δ_H(800 MHz, $CDCl_3$) 5.88–5.82 (1H, m), 5.78–5.70 (3H, m), 5.70–5.62 (1H, m, H-6a), 4.65 (1H, br t, *J* 7.5, H-13a), 2.95–2.86 (1H, m), 2.84 (1H, dd, *J* 13.5, 6.4), 2.56–2.47 (2H, br), 2.46–2.36 (3H, m), 2.35–2.26 (2H, m) and 2.22–2.20 (1H, m); δ_C(100 MHz, $CDCl_3$) 175.9 and 174.7 (C-2 and C-8), 132.4, 131.6, 129.0 and 128.3 (C-11, C-12, C-5 and C-6), 78.6 (C-13a), 75.3 (C-6a), 37.6, 34.2, 30.9, 24.9 and 24.3 (C-3, C-4, C-13, C-10 and C-9); *m/z* (CI, NH_3) 254 [$(M + NH_4)^+$, 100%)] [Found: $(M + NH_4)^+$, *m/z* 254.1393. $C_{13}H_{20}O_4N$ requires *m/z* 254.1392].

1 E. Alvarez, M. L. Candenas, R. Perez, J. L. Ravelo and J. D. Martin, *Chem. Rev.*, 1995, **95**, 1953.
2 K. C. Nicolaou, Z. Yang, G. Q. Shi, J. L. Gunzner, K. A. Agrios and P. Gartner, *Nature*,1998, **392**, 264.
3 K. C. Nicolaou, J. L. Gunzner, G. Q. Shi, K. A. Agrios, P. Gartner and Z. Yang, *Chem. Eur. J.*, 1999, **5**, 646 and references therein.
4 M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4175 and references therein.
5 N. R. Curtis and A. B. Holmes, *Tetrahedron Lett.*, 1992, **33**, 675.
6 N. R. Curtis, A. B. Holmes and M. G. Looney, *Tetrahedron Lett.*, 1992, **33**, 671.
7 J. W. Burton, J. S. Clark, S. Derrer, T. C. Stork, J. G. Bendall and A. B. Holmes, *J. Am. Chem. Soc.*, 1997, **119**, 7483.
8 M. Frigerio and M. Santagostino, *Tetrahedron Lett.*, 1994, **35**, 8019.
9 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
10 M. S. Congreve, A. B. Holmes, A. B. Hughes and M. G. Looney, *J. Am. Chem. Soc.*, 1993, **115**, 5815.
11 A. Fürstner, *Chem. Rev.*, 1999, **99**, 991.

Communication b000303o