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Construction of the 11-oxabicyclo[6.2.1]undecane core of the cladiellins by a novel rearrangement reaction

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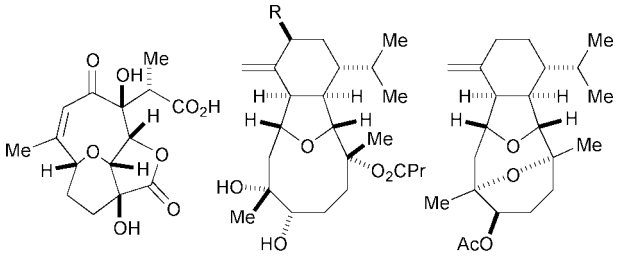
A novel approach to the stereoselective synthesis of the 11-oxabicyclo[6.2.1]undecane system found in the cladiellin (eunicellin) family of marine natural products is described.

Cladiellins (eunicellins) such as litophynin E,[1a] litophynin I[1b] and sclerophytin B[2] are highly oxygenated marine natural products that are part of a much larger family of cembranoids also comprising the briarellins, sacrodictyins and asbestinins.[3] Members of this family of natural products share an oxabicyclo[6.2.1]undecane sub-structure, and many of them possess potent anti-cancer, anti-inflammatory, insecticidal or anti-mollusc activity.[3]

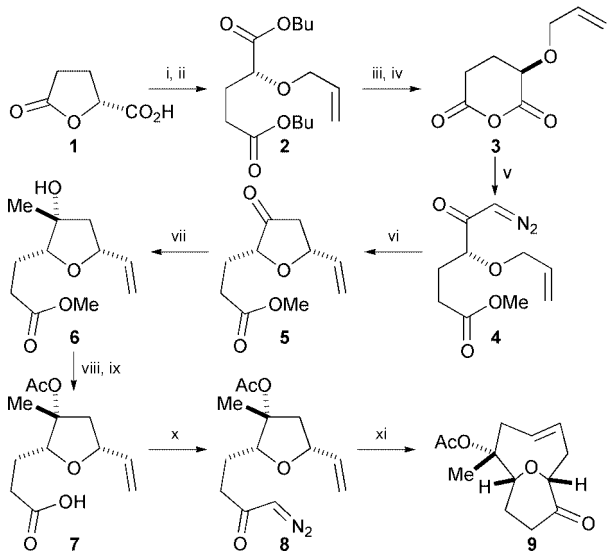


In the course of our research programme directed towards the synthesis of the highly oxygenated sesquiterpene neoliacinic acid,[4,5] we have discovered that it is possible to effect an unusual rearrangement reaction of the oxabicyclo[5.3.1]undecane system of this terrestrial natural product to give the oxabicyclo[6.2.1]undecane system found in the marine cembranoids. We now present the results of our studies and demonstrate that the reaction can be used to prepare the core structure of litophynins E and I.

The (*E*)-bicyclo[5.3.1]bicycloundecene **9**† required for our rearrangement studies was prepared from the commercially available compound (*R*)-γ-butyrolactone-γ-carboxylic acid **1**, which we obtained from (*R*)-glutamic acid (Scheme 1).[6] Ring opening of the lactone **1** was effected using a sub-stoichiometric amount of 10-camphorsulfonic acid (CSA) in a mixture of *n*-butanol and toluene at reflux,[7] and the resulting diester was then converted into the allyl ether **2** by silver(I) oxide promoted alkylation of the free hydroxy group with excess allyl bromide.[8] Saponification of the diester **2** and treatment of the resulting diacid with acetic anhydride provided the substituted glutaric anhydride **3**. Reaction of the cyclic anhydride **3** with a large excess of diazomethane resulted in contrasteric opening of the ring to afford the diazoketone **4** in reasonable yield, without formation of the other possible regioisomeric diazoketone product.‡ The diazoketone **4** was then treated with a sub-stoichiometric amount of $Rh_2(O_2CCPh_3)_4$, which delivered the 3(2*H*)-furanone **5** resulting from intramolecular C–H addition of the intermediate rhodium carbenoid.[4,9] Regioselective and stereoselective introduction of a methyl substituent was accomplished by treatment of the ketone **5** with trimethylaluminium at low temperature.[4,10] At this stage, some of the lactone produced by transesterification of the methyl ester with the tertiary alcohol was obtained, but the process was reversed by treatment of the mixture with triethylamine in methanol at reflux. The tertiary alcohol **6** was converted into the acid **7** by sequential acetylation and selective hydrolysis of the methyl ester, and the carboxylic acid **7** was then transformed into the diazoketone **8**. Treatment of the diazoketone **8** with copper(II) hexafluoroacetylacetonate generated an electrophilic copper carbenoid that underwent tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement with ring expansion.[11] The reaction delivered the strained bridged-bicyclic ether **9** containing an (*E*)-alkene as the key intermediate.[4b] The corresponding (*Z*)-alkene isomer was prepared in 79% yield by treatment of **9** with AIBN and a sub-stoichiometric amount of ethanethiol in benzene at reflux.[4a]

It was immediately apparent that the rather unstable (*E*)-alkene **9** had unusual reactivity. Attempted epoxidation of the alkene **9** with *m*-CPBA in dichloromethane at reflux afforded a complex mixture of products and delivered a major compound that contained an *m*-chlorobenzoate group rather than the expected epoxide. In contrast, the (*Z*)-alkene isomer of **9** underwent conventional epoxidation under identical conditions to deliver the expected product as a *ca.* 3:1 mixture of diastereoisomers. Attempted epoxidation of the (*E*)-alkene **9** with milder oxidants such as DMDO also failed to yield the expected epoxide.

We suspected that the unusual reactivity of the (*E*)-alkene **9** was due to transannular reaction of the bridging ether oxygen,



Scheme 1 *Reagents and conditions*: i, Bu^{n}OH, CSA (cat.), PhMe, Dean–Stark, reflux (78%); ii, CH_2CHCH_2Br, Ag_2O, Et_2O, reflux (89%); iii, LiOH, THF, H_2O, reflux; iv, Ac_2O, reflux (83% over two steps); v, CH_2N_2, 0 °C → r.t., CH_2Cl_2–Et_2O (59%); vi, $Rh_2(O_2CCPh_3)_4$, CH_2Cl_2, r.t. (50%); vii, $AlMe_3$, CH_2Cl_2, −78 → −10 °C, then Et_3N, MeOH, reflux (71%); viii, Ac_2O, DMAP, CH_2Cl_2, r.t. (88%); ix, K_2CO_3, MeOH, H_2O, r.t.; x, $(COCl)_2$, CH_2Cl_2, r.t., then CH_2N_2, Et_2O, CH_2Cl_2, 0 °C (67% over two steps); xi, $Cu(hfacac)_2$, CH_2Cl_2, reflux (50%).

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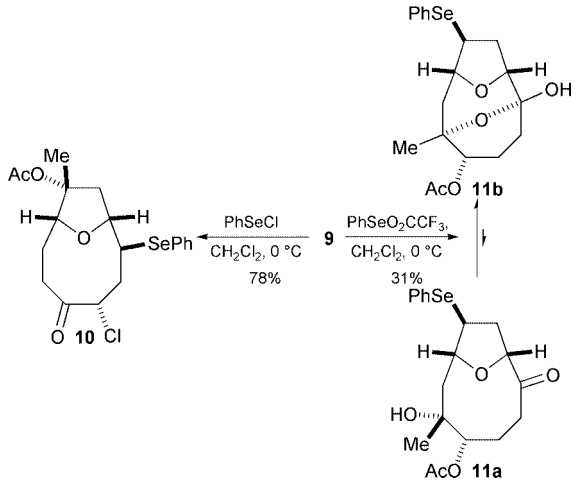
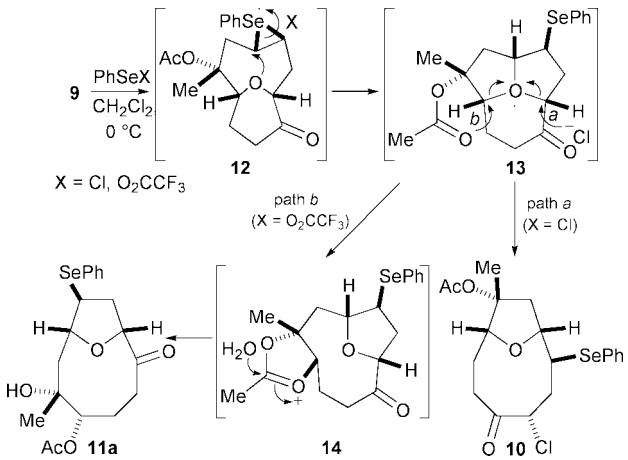


Scheme 2

which is forced to lie in close proximity to the alkene. In order to probe the reactivity of **9**, we investigated the reaction of this compound with electrophilic selenium reagents. Upon treatment with phenylselenenyl chloride, the *E* alkene **9** underwent rearrangement to provide the crystalline oxabicyclo[6.2.1]undecane **10** in good yield. In contrast, treatment of the (*E*)-alkene **9** with phenylselenenyl trifluoroacetate afforded the crystalline rearrangement product **11** in moderate yield. The structures of both the rearrangement products **10** and **11** were confirmed by X-ray crystallography;§ the rearrangement product **11** was found to exist as the hemiacetal **11b**¶ rather than the ring-opened tautomer **11a** in both the solid state and in solution. It is significant that the (*Z*)-isomer of the alkene **9** did not undergo rearrangement when treated with either selenium reagent, but instead reacted to give complex mixtures of products.

The formation of the rearranged bridged-bicyclic ethers **10** and **11** can be accounted for as shown in Scheme 3. Reaction of alkene **9** with either electrophilic selenium reagent results in stereoselective formation of the selenonium ion **12** and subsequent transannular attack of the bridging ether oxygen atom affords the tricyclic oxonium ion **13**. In the presence of chloride ion, nucleophilic attack occurs at the electrophilic site α to the carbonyl group (path *a*) and the bridged-bicyclic ether **10** is produced. In the presence of trifluoroacetate ion, the oxonium intermediate **13** does not suffer immediate attack by the weakly nucleophilic counterion. Instead, the acetate group participates in intramolecular S_N2 opening of the tricyclic oxonium ion (path *b*), and the oxonium intermediate **14** is produced. The ion **14** probably survives until work up, at which



Scheme 3

stage water attacks and the acetate group is transferred from the tertiary site to the less sterically congested secondary hydroxy group.

The rearrangement product **11a** contains most of the functionality that adorns the oxygen-bridged core of litophynins E and I.[1] The compound also possesses the correct absolute and relative configuration at the four oxygen-bearing stereogenic centres. Thus, we have prepared an advanced intermediate for the synthesis of litophynins E and I in 12 steps from the commercially available compound (*R*)-γ-butyrolactone-γ-carboxylic acid **1** (Scheme 1).

We are currently exploring the optimisation of the rearrangement reaction (**9** → **11**, Scheme 3), completion of the synthesis of litophynins E and I, and elaboration of tautomer **11b** to give sclerophytin B. The results of these studies will be reported in due course.

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Notes and references

† Compound **9** has been prepared by us using an alternative route [see ref. 4*b*)].

‡ The only other product obtained was the dimethyl ester (9%) resulting from hydrolysis of the anhydride **3** and esterification of the resulting diacid.

§ *Crystal data*: **10**: $C_{19}H_{23}ClO_4Se$, M + 429.78, monoclinic, space group $P2_1$, a = 5.2491(2), b = 21.3577(10), c = 16.4109(8) Å, β = 90.709(3)°, V = 1839.66(14) Å^3, Z = 4, μ = 2.207 mm^{-1}, T = 150(2) K, 12 2734 reflections collected of which 6208 (R_{int} = 0.101) were independent and 4081 [$I > 2\sigma(I)$] were observed; $R1$ [$I > 2\sigma(I)$] = 0.0583, $wR2$[$I > 2\sigma(I)$] = 0.0894.

11b: $C_{19}H_{24}O_5Se$, M = 411.34, monoclinic, space group $P2_1$, a = 6.0174(8), b = 20.717(3), c = 7.6596(10) Å, β = 108.215(3)°, V = 907.0(2) Å^3, Z = 2, μ = 2.096 mm^{-1}, T = 150(2) K, 3210 independent reflections collected of which 2792 [$I > 2\sigma(I)$] were observed; $R1$ [$I > 2\sigma(I)$] = 0.0278, $wR2$ [$I > 2\sigma(I)$] = 0.568.

CCDC 182/1635. See http://www.rsc.org/suppdata/cc/b0/b002511i/ for crystallographic data in .cif format.

¶ *Selected data* for **11b**: mp 119–120 °C (Found: C, 55.44; H, 5.73. $C_{19}H_{24}O_5Se$ requires C, 55.48; H, 5.88%); ν_{max}($CHCl_3$)/cm^{-1} 3590, 2938, 1729, 1374, 1103, 1046, 990, 972; δ_H(500 MHz; $CDCl_3$) 1.21 (3H, s), 1.66–1.84 (3H, m), 1.94–2.05 (3H, m), 2.10 (3H, s), 2.38 (1H, br), 2.63–2.70 (1H, m), 2.84 (1H, dd, *J* 8.9, 13.4 Hz), 4.00 (1H, ddd, *J* 3.6, 8.4, 8.4 Hz), 4.19 (1H, d, *J* 7.5 Hz), 4.44–4.47 (1H, m), 4.52–4.54 (1H, m), 7.26–7.30 (3H, m), 7.57–7.59 (2H, m); δ_C(126 MHz; $CDCl_3$) 21.1(q), 22.9(t), 29.9(q), 30.6(t), 35.4(t), 43.4(d), 46.1(t), 72.2(d), 76.1(s), 85.0(d), 87.2(d), 96.8(s), 127.8(d), 129.2(d), 129.6(s), 134.4(d), 170.5(s); MS (EI) *m/z* 412 (M^+, 14%), 410(9), 408(4), 255(22), 195(50), 157(27), 85(53), 43(100) (Found: M^+, 412.0789. $C_{19}H_{24}O_5{}^{80}Se$ requires M, 412.0789).

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