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The first total synthesis of sequosempervirin A through an orthoester Claisen rearrangement—ring closing metathesis sequence

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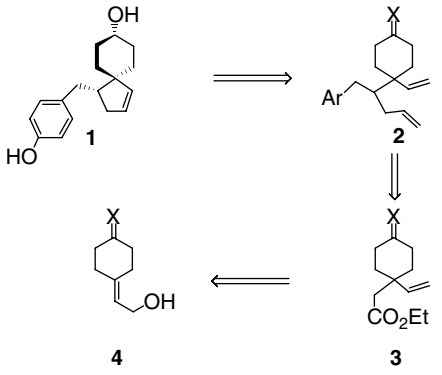
Abstract—The first total synthesis of sequosempervirin A, a norlignan with a unique spirocyclic structure has been accomplished using an orthoester Claisen rearrangement—ring closing metathesis sequence.

Sequosempervirin A **1** is the first naturally occurring norlignan possessing an unusual [4.5] decane ring system. It was isolated[1] from *Sequoia sempervirens*, a species of the taxodiaceae family. A variety of compounds such as terpenoids,[2] lignans[3] and flavonones[4] have earlier been isolated from taxodiaceae. Some of these compounds showed antifungal,[5] antibacterial[6] and antitumour[7] activity. Thus, sequosempervirin A is also expected to exhibit useful bioactivity, however, as yet, none has been reported. We initiated a program to develop a flexible strategy for the synthesis of this structurally unique compound and its structural analogues in order to evaluate their biological activities. We herein report the first total synthesis of sequosempervirin A.

The key step in our strategy is the synthesis of the spirocycle through ring closing metathesis (RCM)[8] of diene **2** prepared from an appropriately substituted cyclohexane derivative. Diene **2** may be available by elaboration of cyclohexane derivative **3**, which in turn should be available from orthoester Claisen rearrangement of allyl alcohol **4** (Scheme 1).

Our initial target was to generate a diene analogous to structure **2**. The synthesis began with Horner–Wadsworth–Emmons olefination of the cyclohexanone derivative **5**[9] with triethyl phosphonoacetate (TEPA) to produce the unsaturated ester **6** in 84% yield (Scheme 2).[10] Lithium aluminum hydride reduction of ester **6** at rt produced alcohol **7** in 86% yield. Orthoester Claisen rearrangement of allylic alcohol **7** was achieved at 140 °C to produce the unsaturated ester **8**. Alkylation of the lithium enolate generated from ester **8** with *p*-methoxybenzyl bromide afforded ester **9** in excellent yield. Ester **9** was then transformed into aldehyde **10** through a sequence of reduction ($LiAlH_4$) and Swern oxidation. The addition of vinyl magnesium bromide to aldehyde **10** gave a single diastereomer of the dienol **12** in 80% yield as revealed by ^1H and ^{13}C NMR spectroscopy. The stereochemical assignment of dienol **12** follows from addition of vinyl magnesium bromide to the carbonyl group using Cram's model. For removal of the hydroxyl group we explored the possibility of radical induced cleavage of xanthate **13**. Surprisingly,



Scheme 1.

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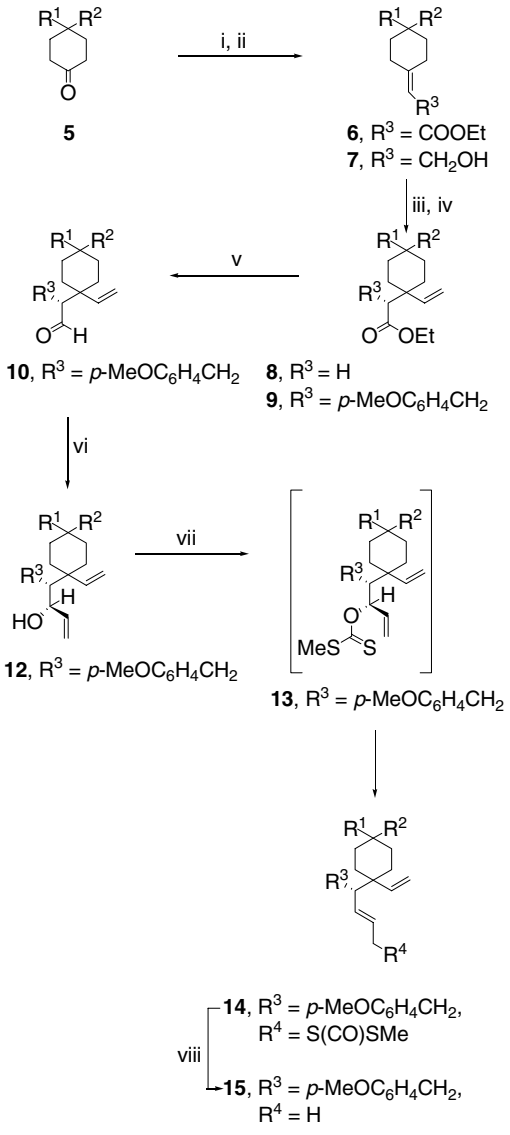


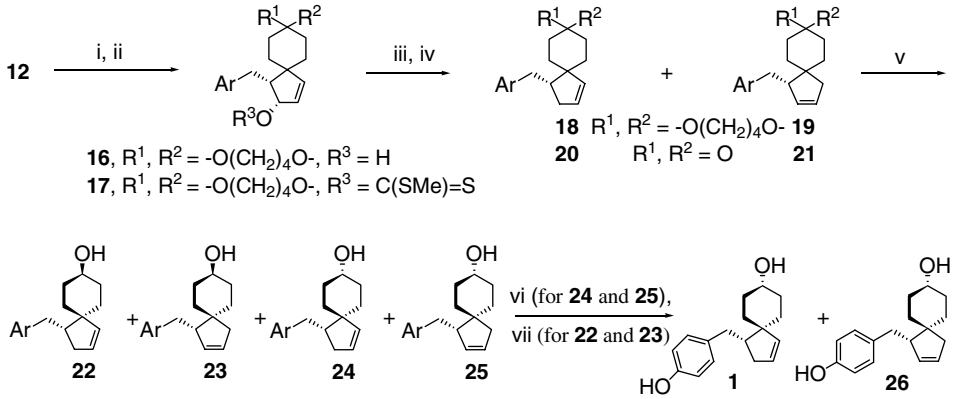
Scheme 2. Reagents and conditions: (i) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, rt, 84%; (ii) $LiAlH_4$, Et_2O, rt, 1 h, 86%; (iii) $(OEt)_3CCH_3$, propionic acid, xylene, 140 °C, 3 h, 66%; (iv) LDA, *p*-$MeOC_6H_4CH_2Br$, THF, 0 °C, 93%; (v) (a) $LiAlH_4$, Et_2O, (0 °C→rt), 1 h, 88%, (b) oxalyl chloride, DMSO, Et_3N, DCM, −78 °C, 73%; (vi) CH_2=CHMgBr, THF, 0 °C, 1 h, 80%; (vii) NaH, CS_2, MeI, THF, (0 °C→rt), 6 h, 70%; (viii) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 2 h, (78%).

attempts to prepare xanthate **13** using the conventional procedure (NaH–THF, CS_2, 0 °C→rt) led to the isolation of dithiocarbonate **14**, exclusively, in excellent yield. The structure of this compound was easily determined by the appearance of a single olefinic CH_2 at δ 115.9 instead of the two olefinic CH_2's expected for xanthate **13**. This structure was further confirmed by tributyltin hydride (TBTH) reduction to produce diene **15**. The formation of **14** may be explained by a spontaneous [3.3] rearrangement of the initially formed xanthate **13**. [3.3] Sigmatropic rearrangement of xanthates derived from allylic alcohols have been reported previously[11] and proceed only at an elevated temperature (∼80 °C). The facile rearrangement of xanthate **13** even at 0 °C may be attributed to relief of the strain arising from steric crowding in the vicinity of the reacting centre. Facilitation of the [3.3] rearrangement of the allyl xanthate by steric buttressing, as observed here, is unprecedented.

We then decided to reverse the sequence, that is, first to carry out the RCM of dienol **12** then reductive removal of the hydroxyl group. RCM of dienes possessing secondary hydroxyl groups at the allylic position with Ru-carbene has often been reported to follow non-metathetic processes[12] involving isomerisation of double bonds. Fortunately, RCM of dienol **12** with Grubbs 1st generation catalyst[13] $(PCy_3)_2Cl_2Ru$=CHPh **11**, (4 mol %) proceeded smoothly to give exclusively, spirocycle **16** in 81% yield. The cis-orientation of the hydroxyl and *p*-methoxy benzyl groups in spirocycle **16** was indicated by the coupling constant ($J = 6.3$ Hz) of the proton adjacent to the hydroxyl group[14] thus confirming the stereochemical assignment of dienol **12**. This stereochemical assignment was further confirmed by a positive NOE (1.4%) observed between the proton adjacent to the OH group and the proton adjacent to the benzyl group in cyclopentenol **16**. TBTH reduction of xanthate **17**, prepared from spirocyclopentenol **16**, led to an inseparable mixture of isomeric cyclopentenes **18** and **19** (2:1) in excellent yield. The structures of the cyclopentenes were established by transformation of the mixture of **18** and **19** to sequosempervirin A **1** and *iso*-sequosempervirin A **26**, respectively, as follows. Treatment of the mixture with 3 N HCl effected deketalization to produce a mixture of isomeric cyclopentenes **20** and **21**. Reduction of this mixture of ketones afforded four diastereoisomeric alcohols **22**, **23**, **24** and **25**. Chromatography of this mixture afforded two fractions. The minor fraction ($R_f = 0.5$) (ethyl acetate–petroleum ether) obtained in 34% yield was demethylated[15] with sodium ethanethiolate to produce a mixture of the regioisomeric cyclopentene derivatives which on flash chromatography (silica gel 230–400 mesh) afforded sequosempervirin A **1** in 50% yield and *iso*-sequosempervirin A **26** (23%). Sequosempervirin A **1** prepared in this way had mp 169–170 °C (lit.[1] 172–174 °C). The ^1H and ^{13}C NMR spectral data of the synthetic sample were closely comparable to those reported in the literature.[1] Thus, the minor fraction obtained from reduction of ketones **20** and **21** was a mixture of the regioisomeric cyclopentenes **24** and **25** (Scheme 3).

The major fraction ($R_f = 0.4$) (ethyl acetate–petroleum ether) isolated in 49% yield comprising a mixture of alcohols **22** and **23** could also be converted to sequosempervirin A **1** and *iso*-sequosempervirin A **26** through alcohols **24** and **25** obtained by inversion of the stereochemistry of the hydroxyl group via Mitsunobu reaction. This transformation unequivocally established the stereochemistry of alcohols **22**–**25** obtained from sodium borohydride reduction of ketones **20** and **21**.

In conclusion, we have achieved the first total synthesis of sequosempervirin A **1**. The key steps involve an orthoester Claisen rearrangement of an appropriately functionalized cyclohexane derivative and RCM.[16] This



Scheme 3. Reagents and conditions: (i) **11** (4 mol %), DCM, rt, 6 h, 81%; (ii) NaH, CS_2, MeI, THF, rt, 3.5 h, 60%; (iii) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 1.5 h, 80%; (iv) 3 N HCl, THF, rt, 1 h, 81%; (v) $NaBH_4$, MeOH, 0 °C, 30 min, 49% (mixture of **22** and **23**), 34% (mixture of **24** and **25**); (vi) EtSNa, DMF, 140 °C, 7 h, 50% (for **1**), 23% (for **26**); (vii) (a) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, rt, 3 h, (b) 2 N NaOH, THF, rt, overnight, 53% overall.

approach has also led to the synthesis of *iso*-sequosempervirin A **26** and provides scope for asymmetric induction during the carbonyl reduction step using chiral reducing agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.084.

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10. All new compounds were characterized on the basis of IR, ^1H, ^{13}C NMR and HRMS data. Spectral data for selected compounds: Compound **12**: IR (neat) 3454, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43–1.48 (2H, m, CH_2), 1.52–1.66 (4H, m, CH_2), 1.71–1.86 (6H, m, CH_2), 1.71–1.86 (1H, m, CH), 2.61 (1H, dd, $J = 4.8$, 15.0 Hz, HCH), 2.72 (1H, dd, $J = 6.3$, 15.0 Hz, HCH), 3.63 (4H, br s, OCH_2), 3.76 (3H, s, OCH_3), 4.58 (1H, br s, OCH), 4.94 (1H, d, $J = 10.4$ Hz, =CH), 5.08–5.09 (2H, m, $=CH_2$), 5.32 (1H, d, $J = 11.0$ Hz, =CH), 5.57–5.68 (1H, m, CH=), 5.92 (1H, dd, $J = 11.0$, 17.8 Hz, =CH), 6.76 (2H, d, $J = 8.1$ Hz, Ar–CH), 7.07 (2H, d, $J = 8.1$ Hz, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.9 (CH_2), 29.6 (CH_2), 29.70 (CH_2), 29.71 (CH_2), 29.8 (CH_2), 30.8 (CH_2), 30.9 (CH_2), 43.2 (C), 54.8 (CH), 55.2 (OCH_3), 61.4 (OCH_2), 61.5 (OCH_2), 71.7 (OCH_2), 100.8 (C), 113.4 (CH_2), 113.5 (CH), 115.8 (CH_2), 129.9 (CH), 135.1 (C), 141.3 (CH), 143.6 (CH), 157.4 (C); HRMS *m/z* 409.2392 $[(M+Na)^+$; Calcd for $C_{24}H_{34}O_4Na$: 409.2355]: Compound **16**: IR (neat) 3433, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.29 (2H, m, CH_2), 1.34–1.38 (2H, m, CH_2), 1.39–1.45 (1H, m, CH_2), 1.59–1.67 (4H, m, CH_2), 1.76–1.87 (3H, m, CH_2), 1.76–1.87 (1H, m, CH), 2.52 (1H, t, $J = 13.2$ Hz, CH), 2.84 (1H, dd, $J = 4.8$, 13.4 Hz, CH), 3.63 (2H, br s, OCH_2), 3.69 (2H, br s, OCH_2), 3.77 (3H, s, OCH_3), 4.61 (1H, d, $J = 6.3$ Hz, OCH), 5.69 (1H, d, $J = 5.7$ Hz, =CH), 6.22 (1 H, d, $J = 5.9$ Hz, =CH), 6.83 (2H, d, $J = 8.4$ Hz, Ar–CH), 7.16 (2H, d, $J = 8.4$ Hz, Ar–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6 (CH_2), 29.8 (CH_2), 30.3 (CH_2), 30.8 (CH_2), 31.1 (CH_2), 33.7 (CH_2), 34.1 (CH_2), 49.9 (C), 55.2 (OCH_3), 60.3 (CH), 61.6 (OCH_2), 61.7 (OCH_2), 82.0 (OCH), 100.6 (C), 114.2 (CH), 129.7 (CH), 132.3 (CH), 133.1(C), 138.9 (CH), 157.9 (C); HRMS *m/z* 381.2038 $[(M+Na)^+$; Calcd for $C_{22}H_{30}O_4Na$: 381.2042]: Compound **1**: mp = 169–170 °C; ^1H NMR (300 MHz, CD_3OD): δ 1.18–1.19 (1H, m, CH), 1.29–1.31 (1H, m, CH), 1.55–1.64 (1H, m, CH_2), 1.69–1.71 (2H, m, CH_2), 1.81–1.86 (3H, m, CH_2), 1.99–2.05 (1H, m, CH), 1.99–2.05 (1H, m, CH_2), 2.15–2.16 (1H, m, CH_2), 2.25 (1H, t, $J = 12.68$ Hz, CH_2), 2.79 (1H, dd, $J = 2.84$, 13.3 Hz, CH_2), 3.84–3.86 (1H, m, OCH), 5.62–5.64 (1H, m, =CH), 5.86 (1H, d, $J = 5.67$ Hz, =CH), 6.68 (2H, d, $J = 8.37$ Hz, Ar–CH), 6.97 (2H, d, $J = 8.34$ Hz, Ar–CH); ^{13}C NMR (75 MHz, CD_3OD): δ 28.1 (CH_2), 31.5 (CH_2), 32.2 (CH_2), 33.0 (CH_2), 36.1 (CH_2), 37.5 (CH_2), 50.6 (CH), 50.9 (C), 68.3 (CH), 116.0 (CH), 129.3 (CH), 130.7

(CH), 134.2 (C), 139.6 (CH), 156.3 (C); HRMS *m/z* 281.1509 [(M+Na)$^+$; Calcd for $C_{17}H_{22}O_2Na$: 281.1517].

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