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Alkoxy group facilitated ring closing metathesis (RCM) of acyclic 1,6-dienes. Convenient synthesis of non-racemic highly substituted cyclopentenols

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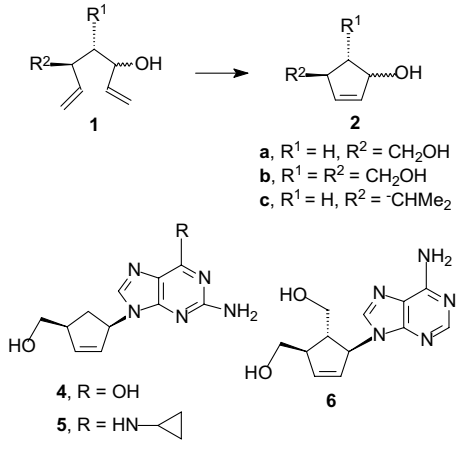
Abstract—Alkoxymethyl groups at the C-5 allylic position of 1,6-dienols have been found to accelerate RCM reactions significantly with the Grubbs' catalyst $PhCH{=}Ru(PCy_3)_2Cl_2$. This phenomenon has been used for direct access to highly substituted cyclopentenols, potential intermediates in the synthesis of carbovir, abacavir and BCA.

The synthesis of cyclopentenols **2** (Scheme 1) in enantiomerically pure form is of considerable importance. The cyclopentenol **2a** represents the carbocyclic moiety of the nucleosides[1] carbovir **4**[2] and abacavir **5**,[3] while the cyclopentenol **2b** has the carbocyclic moiety present in bis(hydroxymethyl)cyclopentenyl adenine (BCA) **6**.[4] (−)-Abacavir has recently been introduced as a drug to combat AIDS while (−)-carbovir and (−)-BCA are potential inhibitors of HIV reverse transcriptase, the causative agent of AIDS. As part of our interest[5] in the synthesis of enantiopure cyclic compounds by using the ring closing metathesis reaction[6] of sugar-derived dienes, we anticipated that RCM of the acyclic-1,6-dienols with Grubbs' catalyst, $PhCH{=}Ru(PCy_3)_2Cl_2$ **3** would provide direct access to the carbocyclic cores present in nucleosides **4** to **6**. Unlike the facile RCM of acyclic-1,7-dienols,[7] the success of RCM of acyclic-1,6-dienols with the catalyst **3** is influenced to a great extent by the substituents. The 1,6-dienes investigated so far either possess a ring or geminal or vicinal substitutents. In these cases the alkene units are conformationally predisposed to ring closure presumably either due to the pre-existing ring,[8] the Thorpe–Ingold effect[9] of the geminal substituents or by *gauche* interaction[3,9,10] of the vicinal substituents and RCM proceeds smoothly to form the cyclopentenols. However there has been no systematic investigation on the RCM of 1,6-dienes **1** where the above conformational preferences are absent. Hoye and Zhao[11] have recently demonstrated that an alkyl or alkoxy substituent at the allylic position, that increases steric crowding, retards RCM whilst a tertiary hydroxyl group at the allylic position significantly accelerates RCM. However, a secondary hydroxyl group at the allylic position adversely affects[7b,11] metathesis reducing the yields of the RCM products through reductive elimination of the enolyl ruthenium hydride arising from tautomerisation of the initially formed Ru–carbene. We now report that the RCM of acyclic-1,6-dienes of



Scheme 1.

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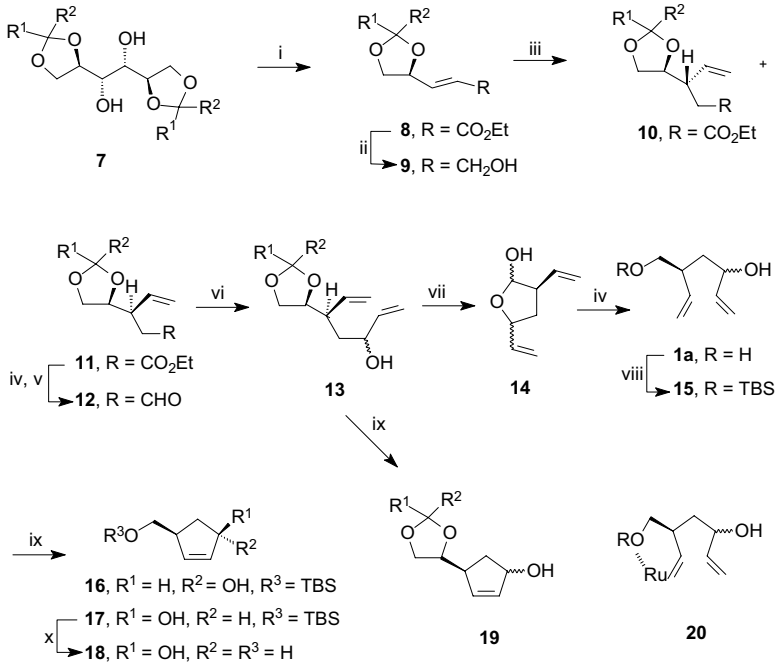
general structure **1** possessing a secondary OH at one allylic centre and an alkyl group at the other allylic centre, both of which deter RCM, can be made to undergo smooth ring closure with the catalyst **3** by installing Ru carbene stabilising element within the R^2 substituent leading to the facile synthesis of the carbocyclic cores of carbovir, abacavir and BCA.

The optically pure diene **1a** was prepared from 1,2:5,6-di-*O*-cyclohexylidine D-mannitol **7**[12] (Scheme 2). Wittig–Horner reaction of the in situ generated aldehyde from periodate cleavage of the diol **7** with triethyl phosphonoacetate afforded the unsaturated ester **8**,[13] which was reduced with $LiAlH_4$ to give the alcohol **9**. Orthoester Claisen rearrangement of the unsaturated alcohol **9** gave a mixture of the unsaturated esters **10** and **11** in a ca. 1:1 ratio. Compounds **10** and **11** were separated by flash chromatography. The stereochemical assignment of the esters **10** and **11** was made by transformation of the latter to the (−)-cyclopentenols **16** and **17** of known absolute configuration as detailed below. The ester **11** was converted to the aldehyde **12** through $LiAlH_4$ reduction followed by Swern oxidation of the resulting alcohol. Addition of vinyl magnesium bromide to the aldehyde **12** produced a 1:1 diastereomeric mixture of the dienols **13**. Regeneration of the vicinal diol from the ketal **13** followed by periodate cleavage afforded the lactol **14** $LiAlH_4$ reduction of which provided the dienol **1a**.

Treatment of the dienol **1a** with 6 mol% of catalyst **3** either in CH_2Cl_2 at rt for 24 h or in refluxing benzene produced an intractable mixture from which the cyclised product **2a** could not be isolated. Surprisingly, the bulkier silyl ether analogue **15** under identical conditions underwent smooth ring closure to produce a mixture of the cyclopentenols **16** and **17** in 93% yield. Similarly, the dienol **13** smoothly produced a diastereoisomeric mixture of the cyclopentenols **19** in 83% yield under analogous conditions. The dramatic increase in reactivity of the dienols **13** and **15** over the dienol **1a** may be attributed to the stabilisation[14] of the Ru carbene by the oxygen atom present in the ketal **13** and the silyl ether **15** as shown in the structure **20**. This stabilisation probably directs metathesis initiation at the alkene nearest to the alkoxy group and thus overrides the competitive fragmentation due to the allylic secondary OH group. The bulkier alkoxy groups in the dienols **13** and **15** also facilitate dissociation of the oxygen atom from the stabilised Ru–carbene **20** required for subsequent reaction with the second alkene unit. This also explains the lack of reactivity of the dienol **1a** towards RCM.

To understand the role of the alkoxy groups in facilitating RCM, the dienol **1c**[15] was chosen for investigation. The C5-substituent in the dienol **1c** lacks oxygen and imposes a steric effect comparable to the ketal unit in **13** or the silyloxy group in **15**. Reaction of the dienol **1c** in CH_2Cl_2 at rt for 24 h with 6 mol% of the catalyst **3** produced a complex mixture. The ^1H NMR spectrum of this mixture showed a broad singlet at δ 4.85 in addition to a multiplet at δ 4.08 attributed to the C3–H of the starting dienol **1c**. The broad singlet at δ 4.85 was

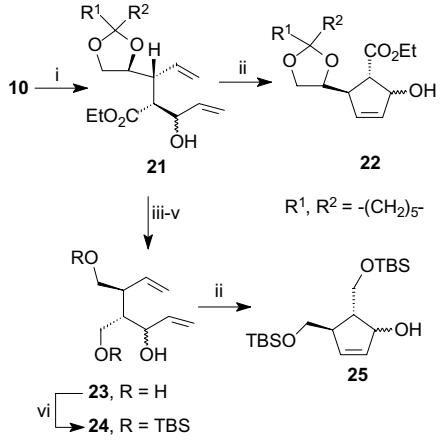


Scheme 2. Reagents and conditions: (i) $NaIO_4$, MeCN/H_2O (3:2), K_2CO_3, $P(O)(OEt)_2CH_2CO_2Et$, 67%; (ii) $LiAlH_4$, Et_2O, −60 °C, 62%; (iii) $CH_3CH(OEt)_3$, propionic acid, 140 °C, 6 h, 68%; (iv) $LiAlH_4$, Et_2O, rt, 92%; (v) oxalyl chloride, DMSO, Et_3N, 82%; (vi) $CH_2{=}CHMgBr$, THF, 70 °C, 1 h, 74%; (vii) (a) 6 M HCl, THF, 1 h, (b) $NaIO_4$, CH_3CN/H_2O (3:2), 1 h, (76% overall); (viii) TBSCl, DMAP, imidazole, Et_3N, DCM, rt, 36 h, 87%; (ix) $(PCy_3)_2Cl_2RuCHPh$, DCM, rt, 24 h, 93%; (x) TBAF, THF, rt, 1 h, 83%.

assigned to the C1–H of the RCM product **2c** on comparison with the chemical shifts (δ 4.86 and 4.83) of C1–H of the cyclopentenols **16** and **19**. The integration of these two proton signals in the reaction mixture revealed that the ratio of the unreacted dienol **1c** and the RCM product **2c** was 7:3. In addition a carbonyl absorption at ν_{max} 1712 cm^{-1} and a COMe resonance at δ 2.10 ppm suggests the occurrence of a competitive β-elimination process during RCM in accord with the observation of Hoye and Zhao.[11] Thus facile RCM of the dienols **13** and **15** having bulky alkoxy groups compared to the sluggish reactivity of the dienol **1c** lacking an alkoxy group establishes the role of neighbouring bulky alkoxy groups in facilitating the RCM reaction with the Ru-catalyst **3**.

The cyclopentenols **16** and **17** were separated by column chromatography to produce the pure cyclopentenols **16**, $[\alpha]_D^{25}$ −153 (*c* 0.1, $CHCl_3$), (lit.[2c] $[\alpha]_D^{20}$ −134.8 (*c* 2.02, $CHCl_3$) and **17**, $[\alpha]_D^{25}$ −69 (*c* 0.1, $CHCl_3$) in 42% and 38% yields, respectively. The cyclopentenol **16** has already been converted[2c] to (−)-carbovir **4**. Desilylation of **17** provided the cyclopentenol **18**, $[\alpha]_D^{25}$ −45 (*c* 0.1, CH_2Cl_2), (lit.[2d] $[\alpha]_D^{25}$ −44.3 (*c* 1.5, CH_2Cl_2) in 83% yield. The cyclopentenol **18** has also been converted[2d] to (−)-carbovir **4**. A similar sequence starting from the unsaturated ester **10** gave the optical antipodes of the cyclopentenols **16** and **17**.

Additional support in favour of the alkoxy group facilitation of the RCM reactions was obtained from smooth ring closure of the dienols **21** and **23** (Scheme 3). Condensation of the lithium enolate of the ester **10** with acrolein produced a 1:1 diastereoisomeric mixture of the alcohols **21**. The *anti* relationship assignment[15] between the COOEt group and the substituent bearing the ketal unit in the dienols **21** is based on the Houk model[16] for electrophilic addition to alkenes possessing an α-chiral centre. RCM of the dienol **21** in benzene at rt with 6 mol% of the catalyst **3** was complete within 5 h to produce the cyclopentenols **22** as a diastereoisomeric mixture (ca. 1:1) in quantitative yield. Similarly, RCM of the dienol **24**, obtained from the ketal **21** as shown in Scheme 3, was complete in 5 h with the catalyst **3** to produce the cyclopentenol **25** in 79% yield. The dienols **24** with the *anti*-disposed silyloxymethyl groups represent the carbocyclic moiety of BCA.



Scheme 3. Reagents and conditions: (i) LDA, acrolein, 83%; (ii) $(PCy_3)_2Cl_2RuCHPh$, C_6H_6, rt, 5 h, 100% for **22**; 4 h, 79% for **25**; (iii) (a) $AcOH/H_2O$ (4:1), (b) $LiAlH_4$, Et_2O, (64% overall), (iv) $NaIO_4$, $MeOH/H_2O$ (3:1), 1 h, 89%, (v) $LiAlH_4$, Et_2O, 69%, (vi) TBSCl, DMAP, imidazole, Et_3N, DCM, rt, 4 h, 68%.

In conclusion, we have demonstrated the role of neighbouring alkoxy groups in facilitating the RCM reaction of acyclic 1,6-dienes with Grubbs' catalyst **3** leading to the synthesis of the enantiomerically pure carbocyclic cores present in carbovir, abacavir and BCA. This investigation has also accomplished a formal synthesis of (−)-carbovir.

Acknowledgements

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13. All new compounds reported here were duly characterised on the basis of spectroscopic (^{1}H and ^{13}C NMR) and microanalytical (C, H) data. Physical characteristics for selected compounds: 1,3-*syn* diastereoisomer (as revealed by a 1.8% NOE) of the cyclopentenols **19**: $R_f = 0.54$ (EtOAc/hexane 1:1); $[\alpha]_D^{22}$ −90.5 (*c* 5.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (2H, br s), 1.52 (8H, m), 2.23–2.33 (2H, m), 2.27 (1H, dt, $J = 14$, 7.6 Hz), 3.66 (1H, t, $J = 7$ Hz), 3.99 (1H, t, $J = 7$ Hz), 4.08 (1H, q, $J = 6$ Hz), 4.60 (1H, d, $J = 7$ Hz), 5.85 (1H, dd, $J = 5.5$, 1.9 Hz), 5.95–5.98 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (CH_2), 23.8 (CH_2), 24.9 (CH_2), 34.6 (CH_2), 35.7 (CH_2), 36.9 (CH_2), 46.6 (CH), 66.9 (OCH_2), 75.4 (OCH), 77.4 (OCH), 109.7 (C), 132.7 (CH), 136.2 (CH). Compound **22**: $R_f = 0.34$ (EtOAc/hexane 3:7); $[\alpha]_D^{25}$ +5.7 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, $J = 7.1$ Hz), 1.38 (2H, m), 1.54–1.65 (8H, m), 3.00 (1H, t, $J = 6.9$ Hz), 3.44 (1H, m), 3.67 (1H, dd, $J = 6$, 8 Hz), 4.01 (1H, dd, $J = 6.3$, 8 Hz), 4.10 (1H, dd, $J = 6.0$, 12.0 Hz), 4.20 (2H, q, 6.9 Hz), 4.97 (1H, m), 5.90 (1H, m) and 6.03 (1H, dd, $J = 1.6$, 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 23.7 (CH_2), 23.9 (CH_2), 25.1 (CH_2), 34.6 (CH_2), 36.0 (CH_2), 50.1 (CH), 50.4 (CH), 60.9 (OCH_2), 66.9 (OCH_2), 76.6 (OCH), 76.9 (OCH), 109.7 (C), 132.5 (CH), 135.7 (CH), 172.0 (CO). Compound **25**: ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.07–0.05 (12H, m), 0.85 (9H, s), 0.86 (9H, s), 2.05–2.13 (1H, m), 2.65–2.69 (1H, m), 3.05 (1H, d, $J = 5.3$ Hz), 3.41–3.47 (1H, m), 3.52–3.60 (1H, m), 3.79 (1H, dd, $J = 7.0$, 10.0 Hz), 3.92 (1H, dd, $J = 4.8$, 10 Hz), 4.86 (1H, m), 5.83 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2 (CH_3), −5.0 (CH_3), 18.4 (C), 18.6 (C), 26.16 (CH_3), 26.24 (CH_3), 46.8 (CH), 50.5 (CH), 63.6 (OCH_2), 66.8 (OCH_2), 78.5 (OCH), 134.2 (CH), 136.1 (CH).
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