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A concise synthesis of the functionalised cyclopentane unit in the antitumoural antibiotic viridenomycin

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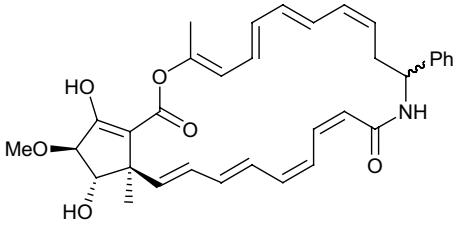
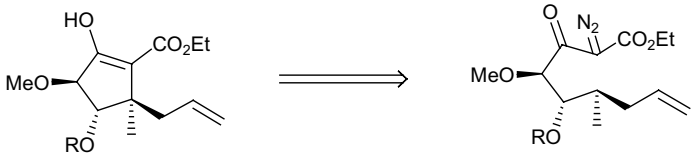
Abstract—A concise seven-step synthesis of the cyclopentane unit in viridenomycin, which uses a regio- and stereo-selective rhodium catalysed intramolecular C–H insertion reaction as the key step, is described.

The polyene macrolactam viridenomycin **1** isolated from the culture broth of the actinomycetes *Streptomyces gannmycicus* and *S. viridochromogenes* is an interesting antitumoural antibiotic substance which prolongs the life of mice with B16 melanoma.[1] The compound is related structurally to the macrolactam hitachimycin,[2] and several oxygenated cyclopentanes have been isolated from microorganisms including pentenomycins,[3] methylenomycins,[4] sarkomycin[5] and terrein.[6] It is likely that these antibiotic antitumoural compounds share a common biosynthetic origin involving cyclisations of modified poly β-ketide precursors,[7] in some instances with ring contraction of 6-ring (aromatic/quinonoid) intermediates.[8] Our interest in the synthesis of, and biogenetic interrelationships between, families of, naturally occurring cyclopentanes has attracted us to the synthesis of viridenomycin **1**. Already Arrington and Meyers,[9] Ishihara et al.[10] and Trost and Jiang,[11] have described their approaches to the synthesis of the unusually substituted cyclopentane ring system **2** in viridenomycin. In this paper we describe a concise seven-step synthesis of the cyclopentane unit **2** which uses the ubiquitous



1



2 **3**

Keywords: Viridenomycin; Intramolecular C–H insertion; Diazo ester.
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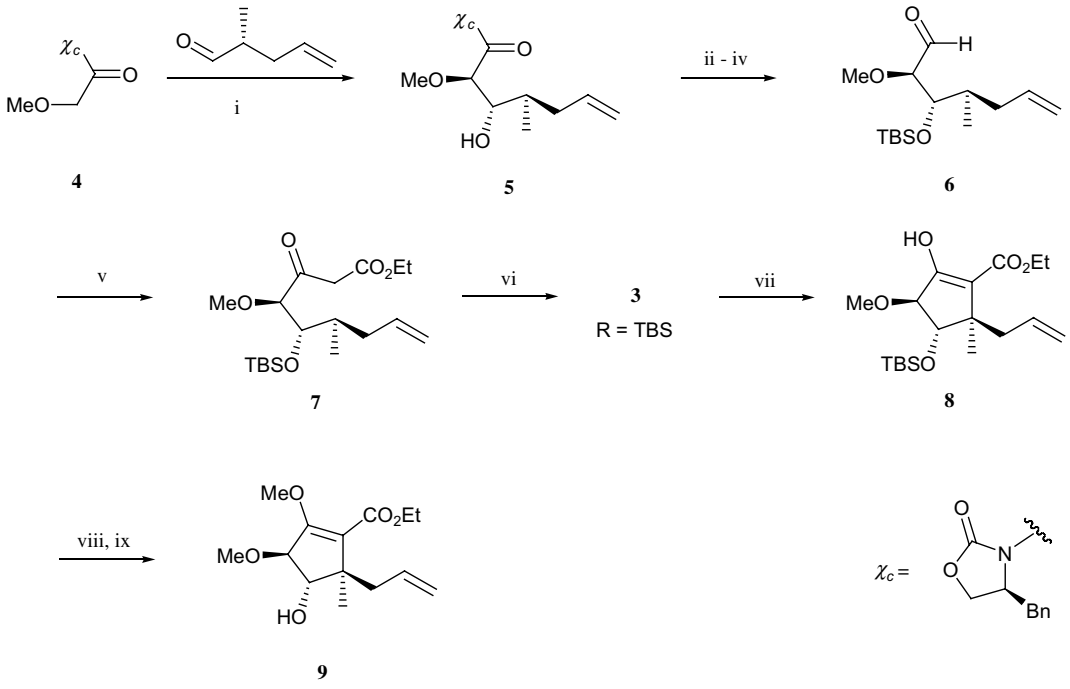

Scheme 1. Reagents and conditions: (i) *n*-Bu_2BOTf, Et_3N, PhMe, −50 °C, 89%; (ii) TBSOTf, 2,6-lutidine, DCM, 0 °C, 80%; (iii) $LiBH_4$ THF, 0 °C–rt, N_2, then H_2O; (iv) $(COCl)_2$, DMSO, DCM, −78 °C, then Et_3N and H_2O; (v) $SnCl_2$, EtO_2CCHN_2, DCM, rt, 89% over three steps; (vi) *p*-acetamidobenzenesulfonylazide (*p*-ABSA), 84%; (vii) 5 mol% $Rh_2(OAc)_4$, DCM, reflux, 62%; (viii) Me_2SO_4, NaH, THF, 84%; (ix) TBAF, THF, 89%.

rhodium-mediated intramolecular C–H insertion, from the diazo ester **3**, as the key reaction[12,13] (see Scheme 1).

Thus, a diastereoselective *syn*-aldol reaction between the Evans substrate **4**[14] and *S*-2-methylpent-4-enal[15] in the presence of *n*-Bu_2BOTf at −50 °C first led to the intermediate **5** in 89% yield. After protection of the *sec*-OH group in **5** as its TBS ether, sequential reduction and oxidation next led to the α-methoxyaldehyde **6**. Treatment of **6** with ethyl diazoacetate–$SnCl_2$[16] then gave the substituted β-keto ester **7**, which was smoothly converted into the corresponding diazo species **3** following treatment with *p*-acetamidobenzenesulfonyl azide and Et_3N.[17] When the diazo β-keto ester **3** (R = TBS) was heated under reflux in DCM in the presence of $Rh_2(OAc)_4$ (5 mol%) it underwent a smooth intramolecular C–H insertion reaction with retention of the absolute configuration[18] and gave the substituted cyclopentane **8** in a satisfying 62% yield. The stereochemistry of **8** was confirmed following methylation to the corresponding methyl ether and deprotection of the TBS group which gave the cyclopentanol **9** as colourless crystals. The X-ray crystal structure of **9** is shown in Figure 1.[19] Our efforts are now being directed towards a total synthesis of viridenomycin and similar highly funtionalised cyclopentane-based macrolactams.

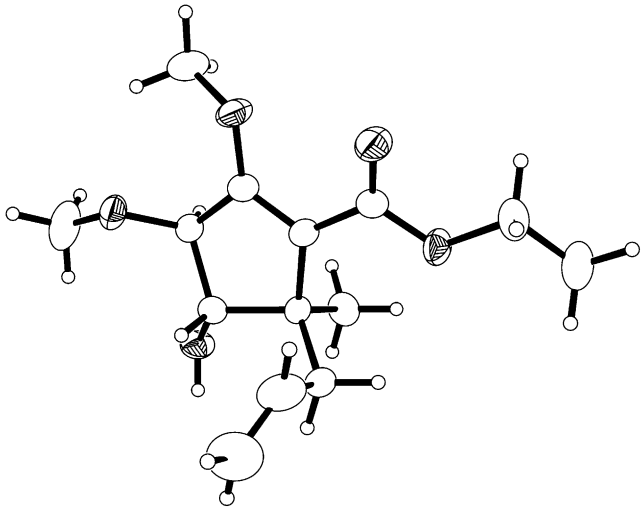

Figure 1. X-ray Structure of the cyclopentanol **9**.

Acknowledgements

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References and notes

1. Hasegawa, T.; Kamiya, T.; Henmi, T.; Iwasaki, H.; Yamatodani, S. *J. Antibiot.* **1975**, *28*, 167–175; Nakagawa, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 659–662.
2. Omura, S.; Nakagawa, A.; Shibata, K.; Sano, H. *Tetrahedron Lett.* **1982**, *23*, 4713–4716.
3. Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot.* **1973**, *26*, 506–512.
4. Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386–392.

5. Umezawa, H.; Yamamoto, T.; Takeuchi, T.; Osato, T.; Okami, Y.; Yamaoka, S.; Okuda, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Umezawa, S. *Antibiot. Chemother.* **1954**, *4*, 514–520.
6. Dunn, A. W.; Entwistle, I. D.; Johnstone, R. A. W. *Phytochemistry* **1975**, *14*, 2081–2082; Barton, D. H. R.; Miller, E. *J. Chem. Soc.* **1955**, 1028–1029.
7. Cf. Hill, R. A.; Carter, R. H.; Staunton, J. *J. Chem Soc., Perkin Trans. 1* **1981**, 2570–2576.
8. See for example: Birch, A. J.; Elliott, P. *Aust. J. Chem.* **1956**, *9*, 95–104; Liu, S.-Y.; Ogihara, Y. *J. Pharm. Soc. Jpn.* **1975**, *95*, 1114–1118; Lee, H. H.; Tan, C. H. *J. Chem. Soc. C* **1967**, 1583–1585, and also Ref. 7.
9. Arrington, M. P.; Meyers, A. I. *Chem. Commun.* **1999**, 1371–1372.
10. Ishihara, J.; Hagihara, K.; Chiba, H.; Ito, K.; Yanagisawa, Y.; Totani, K.; Tadano, K. *Tetrahedron Lett.* **2000**, *41*, 1771–1774.
11. Trost, B. M.; Jiang, C. H. *Org. Lett.* **2003**, *5*, 1563–1 565.
12. Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765–1808; Taber, D. F.; Stiriba, S. E. *Chem. Eur. J.* **1998**, *4*, 990–992; Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808–4809; Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935; Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919–939; Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903; Ye, T.; Mckervey, M. A. *Chem.Rev.* **1994**, *94*, 1091–1160.
13. For an alternative synthesis of the cyclopentane unit in viridenomycin from our laboratory see: Mulholland, N. P.; Pattenden, G. *Tetrahedron Lett.* **2005**, *46*, 937–939.
14. Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775–7778.
15. Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543–572.
16. Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260.
17. Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709–1716.
18. Kaneno, D.; Tomoda, S. *Org. Lett.* **2003**, *5*, 2947–2949; Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547–556; Taber, D. F.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1985**, *26*, 3059–3062; Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196–199; Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686–7693.
19. A colourless tabular crystal of **9** ($0.31 \times 0.15 \times 0.04\ mm^3$) was encapsulated in a film of silicone grease and mounted on a dual-stage glass fibre before transfer to the diffractometer.
Crystal data: $C_{14}H_{22}O_5$, $M = 270.32$, monoclinic, $a = 7.5506$ (13), $b = 8.2729$ (14), $c = 12.416$ (2) Å, $\beta = 104.423(3)^{O}$, $U = 751.1(4)$ Å^3, $T = 150(2)$ K, space group $P\ 2_1$ (No. 4), $Z = 2$, $D_c = 1.195\ g cm^{-3}$, μ(Mo-Kα) = $0.090\ mm^{-1}$, 1835 unique reflections measured and used in all calculations. Final R_1 [1606 $F > 4\sigma(F)$] = 0.0475 and wR [all F^2] was 0.104. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 261952. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].