Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2529–2532

TETRAHEDRON LETTERS

Synthesis of (±)-solanapyrones A and B

Barry Lygo,[a,*] Mohamed Bhatia,[b] Jason W. B. Cooke[c] and David J. Hirst[a]

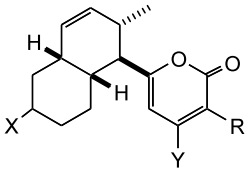
[a]*School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK*
[b]*Department of Chemistry, University of Salford, Salford M5 4WT, UK*
[c]*GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*

Received 12 December 2002; revised 20 January 2003; accepted 31 January 2003

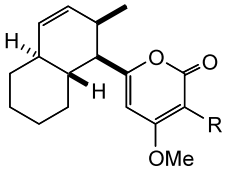
Abstract—In this paper we report the development of a stereoselective IMDA approach to the phytotoxic polyketides (±)-solanapyrones A and B. The stereoselectivity of the key IMDA cycloaddition was optimized by investigating a range of 2,8,10-dodecatrienoic acid derivatives. This established that use of the Weinreb amide led to the desired *exo*-selectivity and also facilitated construction of the pyrone moiety. A novel approach to the installation of the C-3 formyl group in solanapyrone A is also described.

The solanapyrones A–E′ are a family of phytotoxic polyketides that have been isolated from the phytopathogenic fungi *Alternaria solani* and *Ascochyta rabiei*.[1] Solanapyrone C, along with the closely related structures, solanapyrones E–G,[2] has also been isolated from an unidentified marine fungus found on the surface of the green alga *Halimeda monile*.[3] Recently solanapyrone A has been reported to be a selective inhibitor of mammalian DNA polymerase β and λ, suggesting that compounds of this type may have utility in cancer chemotherapy.[4]

solanapyrones



A; X=H, Y=OMe, R=CHO
B; X=H, Y=OMe, R=CH_2OH
C; X=H, Y=$NHCH_2CH_2OH$, R=CHO
E; X=β-OH, Y=NH_2, R=CHO
F; X=α-OH, Y=NH_2, R=CHO
G; X=H, Y=NH_2, R=CHO



D; R=CHO
E'; R=CH_2OH

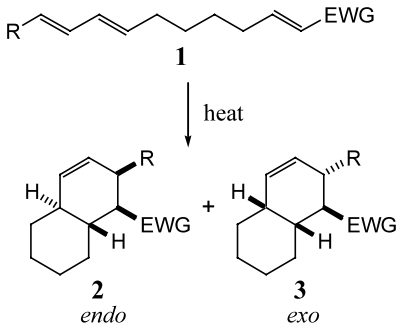
Studies utilizing *A. solani* indicate that the biosynthesis of the majority of these compounds (A–C, E–F) proceeds via an *exo*-selective Diels–Alder cycloaddition.[5,6] Given this, the use of an intramolecular Diels–Alder cycloaddition would seem to be an attractive approach to the synthesis of compounds of this type.[7] Although such an approach has been successfully applied to the stereoselective synthesis of solanapyrone A, this relied on the use of crude enzyme extracts from *A. solani* to promote the key Diels–Alder cycloaddition.[6] To date all other attempts at achieving an *exo*-selective cycloaddition approach to these compounds have proved unsuccessful.[5,6] This highlights a significant limitation in the Diels–Alder chemistry of 1,7,9-decatrienes of type **1**,[8–10] and in this paper we present some observations relevant to this problem.

In the course of developing synthetic approaches to the solanapyrones[11] we examined whether Diels–Alder reactions involving trienes of type **1** could be made *exo*-selective simply by varying the nature of the electron-withdrawing group (EWG) (Scheme 1). There is evidence in the literature to suggest that this may be possible;[8d,9,12] however, studies of this type have not been applied to substrates that are appropriate for the synthesis of the solanapyrones (A–C, E–F).

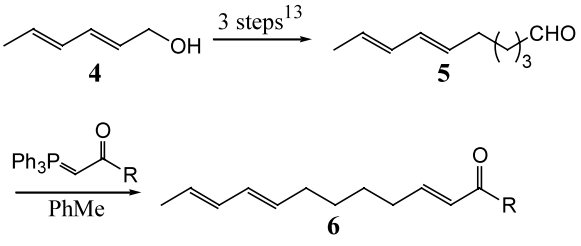
For the purposes of this study we prepared a range of 1,7,9-decatrienes bearing a range of different carbonyl derivatives **6a**–**i**. Compounds **6a**–**e** were prepared by reacting the known aldehyde **5** with an appropriate Wittig reagent (Scheme 2).[6d,8f,13] In all cases the desired 2*E*-alkenes were readily separated from the minor (= 10%) 2*Z*-isomer by-products by chromatography.

* Corresponding author.

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00288-0



Scheme 1.



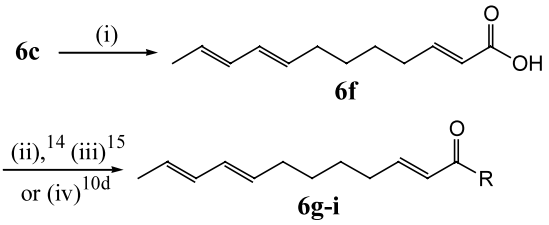
Entry	R	% Yield*
a	*t*-Bu	68
b	OMe	73
c	OEt	87
d	Ot-Bu	83
e	N(Me)OMe	83

* isolated yield of 2*E*-isomer

Scheme 2.

Hydrolysis of ethyl ester **6c** provided the corresponding carboxylic acid **6f** in good yield, and this in turn could be converted into trienes **6g–i** using standard approaches (Scheme 3).[10d,14,15]

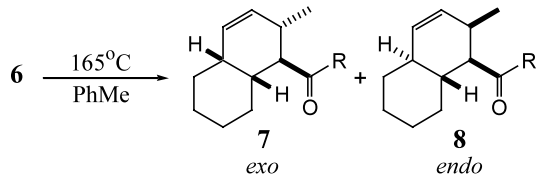
Thermal Diels–Alder reactions involving trienes **6a–i** were then examined (Scheme 4). In all cases the reactions were performed in toluene at ca. 165°C, and all the substrates investigated exhibited similar rates of reaction (reactions were complete in 5–6 days). It was found that ester derivatives **6b–d** generated little or no *endo*/*exo* selectivity. This is entirely in agreement with observations that have been reported for Diels–Alder reactions involving similar triene substrates.[8] Ketone **6a** and carboxylic acid **6f** were similarly non-selective; however, the reactions involving amides **6e**,**g**,**h** and imide **6i** proved to be more interesting. The latter derivative resulted in selectivity for the undesired *endo*-cycloadduct **8i**, whereas amides **6e**,**g**,**h** all favoured the *exo*-adducts **7e**,**g**,**h** with similar levels of selectivity. We could find no evidence of equilibration between the two cycloadducts under the reaction conditions employed.



Entry	R	% Yield*
g	N(Ph)OMe	55
h	NEt_2	90
i		59

* overall yield from **6f**.

Scheme 3. *Reagents and conditions*: (i) 10% aq. LiOH, MeOH, reflux, 96%; (ii) $(COCl)_2$, rt; PhNHOH, aq. $NaHCO_3$, Et_2O, rt; K_2CO_3, MeI, DMF, rt; (iii) *i*-BuOCOCl, NMM, THF, 0°C; Et_2NH, rt; (iv) $(COCl)_2$, rt; 2-oxazolidinone, *n*-BuLi, THF, 0°C.



Entry	R	*exo*:*endo*#	% Yield*
a	*t*-Bu	1:1	64
b	OMe	1:1	85
c	OEt	1:1	82
d	Ot-Bu	1.5:1	84
e	N(Me)OMe	3:1	92
f	OH	1:1	60
g	N(Ph)OMe	3:1	79
h	NEt_2	3:1	86
i		1:2.5	73

estimated by ^{1}H nmr.[16] * isolated yield of *exo*/*endo* mixture.

Scheme 4.

Thus the stereoselectivities obtained are assumed to be kinetic and probably reflect the asynchronous nature of this type of Diels–Alder reaction.[8d,12]

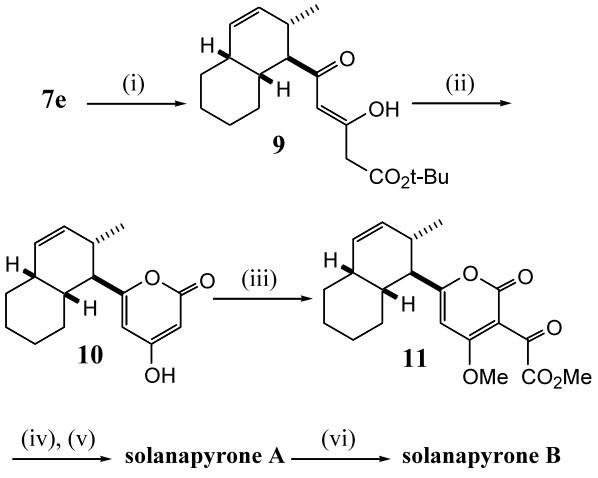
These observations opened up the opportunity to develop a diastereoselective approach to solanapyrones (A–C, E–F). To this end we have investigated the conversion of adduct **7e** into solanapyrones A and B. This particular cycloadduct was chosen because it could

be readily separated from the corresponding *endo*-isomer,[17] and because the Weinreb amide functionality appeared to offer the best means of introducing the pyrone moiety.

It was found that reaction of Weinreb amide **7e** with the dianion derived from *tert*-butyl acetoacetate[18] allowed access to triketide **9**, and that this intermediate could be readily converted into the corresponding 4-hydroxypyrone **10**.[19] Introduction of the C-14 formyl substituent into the pyrone ring of solanapyrone precursors such as **9** is a notorious problem,[6b,7,11] and all attempts at directly introducing this substituent have so far proved unsuccessful. Recently a phenylthiomethylation–Pummerer sequence was successfully applied in the synthesis of solanapyrone D.[7] Here we report an alternative approach which employs the facile O to C rearrangement of a mixed oxalate ester (Scheme 5). Thus treatment of 4-hydroxypyrone **10** with methyl oxalyl chloride in the presence of triethylamine was found to give a *C*-acylated intermediate which could be regioselectively methylated using diazomethane. This provided the key intermediate **11** in good overall yield. This then allowed straightforward access to solanapyrone A via conversion of **11** into the corresponding α-hydroxy acid followed by periodate cleavage.

We have also demonstrated that solanapyrone B can be prepared in good yield simply by reaction of solanapyrone A with sodium borohydride. Samples of solanapyrone A and B prepared in this way had ^{1}H NMR spectra consistent with those previously reported for the natural products.[1]

In conclusion, we have established that 2,8,10-dodecatrienoic acid Weinreb amide **6e** undergoes an *exo*-selective thermal Diels–Alder reaction and that the resulting cycloadduct **7e** can be utilized in the synthesis of solanapyrones A and B.



Scheme 5. *Reagents and conditions*: (i) $CH_3COCH_2CO_2t$-Bu, NaH, THF; *n*-BuLi, 0°C, 81% (50% conv.); (ii) CF_3CO_2H, CH_2Cl_2; Ac_2O; $NaHCO_3$, rt, 63%; (iii) $ClCOCO_2Me$, Et_3N, CH_2Cl_2, rt; CH_2N_2, 83%; (iv) $NaBH_4$, MeOH, rt; aq. NaOH (0.2 M), rt, 70%; (v) $NaIO_4/SiO_2$, CH_2Cl_2, rt, 86%; (vi) $NaBH_4$, MeOH, rt, 79%.

Acknowledgements

We thank the EPSRC for funding and GSK for studentship support (to D.H.).

References

1. (a) Ichihara, A.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett*. **1983**, *24*, 5373; (b) Alam, S. S.; Bilton, J. N.; Slawin, A. M. Z.; Williams, D. J.; Sheppard, R. N.; Strange, R. N. *Phytochemistry* **1989**, *28*, 2627; (c) Oikawa, H.; Yokota, T.; Sakano, C.; Suzuki, Y.; Naya, A.; Ichihara, A. *Biosci. Biotechnol. Biochem*. **1998**, *62*, 2016.
2. Two different structures have been assigned the name solanapyrone E,[1,3] here we use the notation E and E′ to distinguish them.
3. Jenkins, K. M.; Toske, S. G.; Jensen, P. R.; Fenical, W. *Phytochemistry* **1998**, *49*, 2299.
4. Mizushina, Y.; Kamisuki, S.; Kasai, N.; Shimazaki, N.; Takemura, M.; Asahara, H.; Linn, S.; Yoshida, S.; Matsukage, A.; Koiwai, O.; Sugawara, F.; Yoshida, H.; Sakaguchi, K. *J. Biol. Chem*. **2002**, *277*, 630.
5. Oikawa, H.; Suzuki, Y.; Naya, A.; Katayama, K.; Ichihara, A. *J. Am. Chem. Soc*. **1994**, *116*, 3605.
6. (a) Oikawa, H.; Suzuki, Y.; Katayama, K.; Naya, A.; Sakano, C.; Ichihara, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1225; (b) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem*. **1998**, *63*, 8748; (c) Oikawa, H.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Chem. Soc., Chem. Commun*. **1995**, 1321; (d) Ichihara, A.; Miki, M.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett*. **1987**, *28*, 1175.
7. For a non-Diels–Alder approach to the solanapyrones D and E′, see: (a) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uda, H. *J. Org. Chem*. **2002**, *67*, 5969; (b) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M. *Org. Lett*. **2001**, *3*, 251.
8. Thermal Diels–Alder reactions involving substrates of type **1** (EWG=CHO, COR, CO_2R, NO_2) are generally non-selective see for example: (a) Williams, D. R.; Brugel, T. A. *Org. Lett*. **2000**, *2*, 1023; (b) Witter, D. J.; Vederas, J. C. *J. Org. Chem*. **1996**, *61*, 2613; (c) Jung, S. H.; Lee, Y. S.; Park, H.; Kwon, D.-S. *Tetrahedron Lett*. **1995**, *36*, 1051; (d) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S. *Tetrahedron Lett*. **1987**, *28*, 2447; (e) Funk, R. L.; Zeller, W. E. *J. Org. Chem*. **1982**, *47*, 180; (f) Roush, W. R.; Gillis, H. R. *J. Org. Chem*. **1982**, *47*, 4825; (g) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc*. **1981**, *103*, 5200; (h) Joshi, B. S.; Viswanathan, N.; Gawad, D. H.; Balakrishnan, V.; Von Philipsborn, W. *Helv. Chim. Acta* **1975**, *58*, 2295.
9. Thermal Diels–Alder reactions involving substrates of type **1** (EWG=SO_2R, SONR) have been shown to give good levels of *exo*-selectivity, see: (a) Craig, D.; Geach, N. J.; Pearson, C. J.; Salwin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 6071; (b) Craig, D.; Fischer, D. A.; Kemal, O.; Marsh, A.; Plessner, T.; Salwin, A. M. Z.; Williams, D. J. *Tetrahedron* **1991**, *47*, 3095.

10. Lewis and Brønsted acid-catalysed Diels–Alder reactions involving substrates of type **1** generally give good levels of *endo*-selectivity, see for example Refs. 6, 8d, 8f and: (a) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. *Chem. Eur. J.* **2001**, *7*, 4107; (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582; (c) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947; (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238; (e) Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1984**, *49*, 4674.
11. Bhatia, M. Ph.D. Thesis, University of Salford, 2000.
12. (a) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796; (b) Wu, T.-C.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297; (c) Wu, T.-C.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2293.
13. (a) Segi, M.; Takahashi, M.; Nakajima, T.; Suga, S. *Tetrahedron Lett.* **1988**, *29*, 6965; (b) Ichihara, A.; Miki, M.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1987**, *28*, 1175; (c) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
14. Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735.
15. Bernasconi, S.; Comini, A.; Corbella, P.; Gariboldi, M.; Sisti, M. *Synthesis* **1980**, 385.
16. ^{1}H NMR spectra of the *endo*- and *exo*-isomers were initially assigned on the basis of NOE experiments and this was subsequently confirmed by cross-correlation to intermediates **7f**/**8f** and **9**. In addition, the *endo*-isomers **8a**,**b**,**c**,**f**,**i** were generated stereoselectively via Lewis acid-catalysed Diels–Alder reactions and the structure of **8i** confirmed by X-ray crystallography.
17. Compound **7e** can be isolated in 69% yield (from **6e**) after chromatography on silica gel.
18. Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467.
19. Lygo, B. *Tetrahedron* **1995**, *51*, 12859.