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DIENAMINES AS DIELS-ALDER DIENES. AN EFFICIENT SYNTHESIS OF A KEY INTERMEDIATE FOR DRIMANE-RELATED SESQUITERPENES

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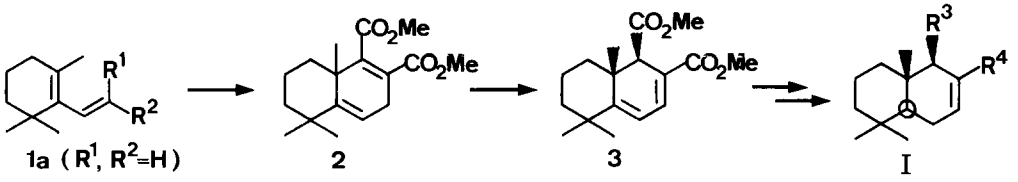
Abstract: An efficient synthesis of dienediester 3, a key intermediate for drimane-related sesquiterpenes, is described starting from enal 4.

Recently there has been increasing interest in the synthesis of biologically active, drimane-related sesquiterpenes having the general structure I[1]. An attractive synthetic approach uses a *Diels-Alder* reaction to construct the appropriately substituted decalin system[1,2]; for example, reaction between 1a and dimethyl acetylenedicarboxylate affords diester 2 which may be converted, *via* a kinetically controlled isomerisation, to diester 3, an important intermediate for access to I[2f] (*cf. Scheme 1*). However, efforts to extend this

Scheme 1

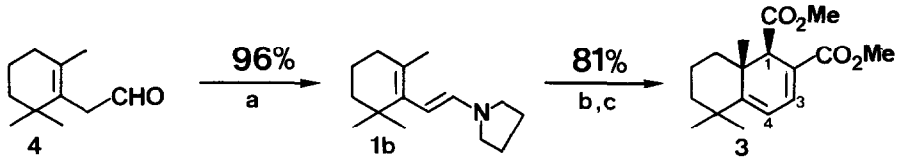


strategy for the synthesis of more functionalised molecules by using other dienes (*i.e.* R^1 or $R^2 \neq H$) have been generally unrewarding[1,2f]. In this context we now present an efficient synthesis of 3 which involves, as the key step, the *Diels-Alder* reaction between the hitherto unreported dienamine 1b (R^1 = H, R^2 = $\overline{N(CH_2)_4}$) and dimethyl fumarate[3].

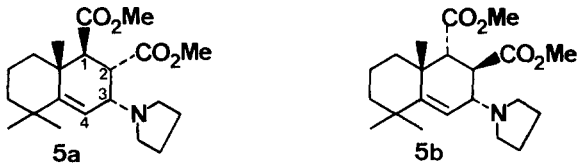
Dienamine 1b (*bp* 105°C/0.7 Torr, *E/Z* ≥99:1), prepared in 96% yield by treatment of the readily available aldehyde 4[4] with pyrrolidine, reacted with dimethyl fumarate[5] in refluxing xylene to give exclusively (≥95%[6]) the cycloadduct 5a[7]. The excellent stereoselectivity of this [4 + 2]-cycloaddition reaction may be rationalised by unfavorable, non-bonding interactions in the transition state leading to the alternative, putative cycloadduct 5b[8]. Elimination of pyrrolidine by heating 5a with acetic anhydride subsequently afforded, in a one-pot procedure, 3 (*mp* 53-54°C[9]) in 81% yield from 1b (*cf. Scheme 2*).

Further *Diels-Alder* reactions of 1b and related dienamines with a variety of dienophiles are under investigation.

Scheme 2



a)  (1.1 mole equiv.)/toluene, 60°C, 1 h; b) $MeO_2C{\cdot}CH\overset{E}{=}CH{\cdot}CO_2Me$ (2 mole equiv.)/xylene, 140°C, 24 h; c) Ac_2O (1.5 mole equiv.)/140°C, 24 h.



References and Notes

[1] D.M. Hollinshead, S.C. Howell, S.V. Ley, M. Mahon, N.M. Ratcliffe & P.A. Worthington, *J.Chem.Soc.Perkin I,* 1579 (1983) and references cited therein.

[2] For other *Diels-Alder* approaches see: a) G. Brieger, *Tetrahedron Lett.*, 4429 (1965); b) J.C. Loperfido, *J.Org.Chem. 38,* 399 (1973); c) J.A. Campos & F.G. Jiminez, *Rev.Soc. Quim.Mex. 19,* 93 (1975); d) S.P. Tanis & K. Nakanishi, *J.Am.Chem.Soc. 101,* 4398 (1979); e) L.P.J. Burton & J.D. White, *J.Am.Chem.Soc. 103,* 3226 (1981); f) M. Jalali-Naini, D. Guillerm & J.-Y. Lallemand, *Tetrahedron 39,* 749 (1983).

[3] For a review of dienamines as *Diels-Alder* dienes, see: M. Petrzilka & J.I. Grayson, *Synthesis,* 753 (1981).

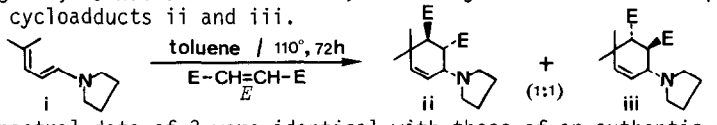
[4] a) O. Isler, M. Montavon, R. Rüegg & P. Zeller, *Helv.Chim.Acta 39,* 259 (1956); b) G.L. Olsen, H.C. Cheung, K.D. Morgan, R. Borer & G. Saucy, *ibid 59,* 567 (1976).

[5] Dimethyl maleate, which rapidly rearranges to the more reactive dimethyl fumarate under the reaction conditions, may also be used.

[6] The absence of cycloadduct 5b (≤5%) in the reaction mixture was ascertained by chromatographic (TLC) and spectroscopic (^{1}H-NMR) analysis.

[7] ^{1}H-NMR (360 MHz, $CDCl_3$): δ 2.76 (*d*, *J* = 13 Hz, H-C(1)); 3.35 (*dd*, *J* = 13 & 7 Hz, H-C(2)); 3.76 (*dd*, *J* = 7 & 4 Hz, H-C(3)); 5.54 (*d*, *J* = 4 Hz, H-C(4)).

[8] In contrast the *Diels-Alder* reaction between (*E*)-4-methyl-1-pyrrolidino-1,3-pentadiene (i) (for the preparation of i, see: H. Leotte, *Rev.Port.Quim. 7(4),* 214 (1965)) and dimethyl fumarate, in which non-bonding interactions in the two possible transition states are negligible, is not stereoselective, affording a *ca.* 1:1 mixture (82% yield) of the diastereomeric cycloadducts ii and iii.



[9] The spectral data of 3 were identical with those of an authentic sample kindly provided by Dr. J.-Y. Lallemand. IR.: 1750, 1720, 1580, 1440, 1280, 1200, 1180, 1030, 1020, 860, 840, 780. ^{1}H-NMR (360 MHz, $CDCl_3$): δ 1.16, 1.18 & 1.20 (3*s*, 9 H); 1.30 - 1.80 (6 H); 3.36 (*d*, *J* = 2.5 Hz, H-C(1)); 3.72 & 3.73 (2*s*, 6 H); 6.01 (*d*, *J* = 6 Hz, H-C(4)); 6.97 (*dd*, *J* = 6 & 2.5 Hz, H-C(3)). ^{13}C-NMR (90.5 MHz, $CDCl_3$): δ 172.9 (*s*); 167.0 (*s*); 161.6 (*s*); 133.9 (*d*); 124.9 (*s*); 117.1 (*d*); 55.6 (*d*); 51.5 (2*q*); 39.4 (*t*); 39.1 (*t*); 38.5 (*s*); 35.7 (*s*); 32.1 (*q*); 31.7 (*q*); 18.8 (*q*); 18.1 (*t*). MS.: 292 (16,M$^+$), 260 (9), 233 (46), 217 (25) 201 (30), 173 (24), 163 (100).

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