Mild Regiospecific Rearrangement of α,β-Unsaturated Ketones into Ring Expanded Annulated Tetrazoles†

Philip Magnus* and G. Mark Taylor
Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

Treatment of the α,β-unsaturated ketones listed in Table 1 with trimethylsilyl azide in the presence of trimethylsilyl triflate gave the ring expanded tetrazole derivatives **8**–**11**.

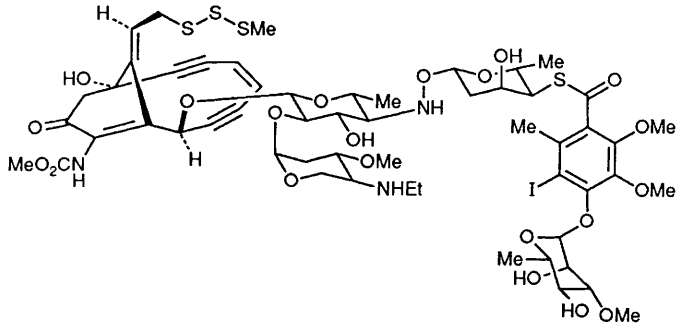
In 1987 the Lederle[1] and Bristol–Myers[2] groups reported the unprecedented structures of calicheamicin γ_1 **1**, esperamicin A_1 **2**, A_{1b} **3**, A_2 **4** and the metabolite esperamicin X **5**, Scheme 1. They were isolated from fermentations of *Micromonospora echinospora* sp. calichensis and cultures of *Actinomadura verrucosospora* BBM 1675, ATCC 39334, respectively. Presently, they are the most potent antitumour antibiotics known, being approximately 10^3 more active than adriamycin against murine tumours and represent a new class of natural products based upon the *Z*-diynene functionality.

During the course of our investigations into the synthesis of these potent antitumour antibiotics[3] we have examined the addition of azide anion and trimethylsilyl azide to the enedione **6** to introduce the nitrogen substituent at C-2. As a prelude to these studies, and because the enedione **6** is considerably more complex, we have examined the reaction of some simple α,β-unsaturated ketones with trimethylsilyl azide.[4,5]

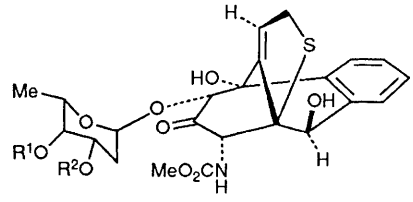
Treatment of the α,β-unsaturated ketones listed in Table 1, with excess of trimethylsilyl azide and trimethylsilyl triflate in dichloromethane at room temperature resulted in regiospecific ring-expansion to give the tetrazoles **8**–**11** in reasonable yields.[6] Only in the case of mesityl oxide was the yield very low, and the tetrazole **7** resulted from alkenyl migration.

Cyclohexenone gave very little of the corresponding ring-expanded tetrazole and owing to purification difficulties was pursued no further. Cyclopentenone did not give any characterisable products. In order to give reasonable yields of the tetrazoles **8**–**11**, it appears that the presence of a β-alkyl group is necessary. This most likely suggests that in the absence of a β-alkyl group the *C*-alkenyl tetrazoles can undergo further

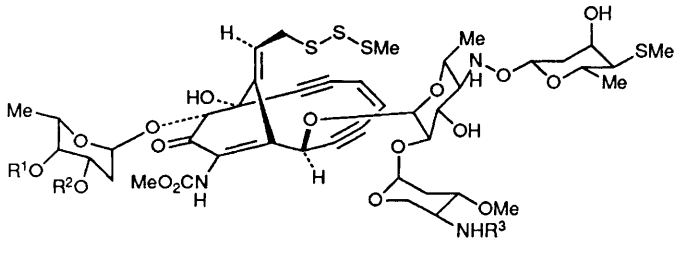
† Submitted to mark the 150th anniversary of the Chemical Society/Royal Society of Chemistry.



1 Calicheamicin γ1

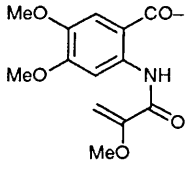


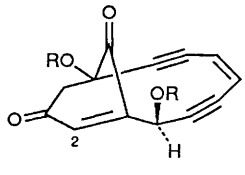
5 Esperamicin X



2 Esperamicin A_1, R^1 = H, R^2 = AC, R^3 = Pr^i
3 Esperamicin A_{1b}, R^1 = AC, R^2 = H, R^3 = Pr^i
4 Esperamicin A_2, R^1 = H, R^2 = AC, R^3 = Et

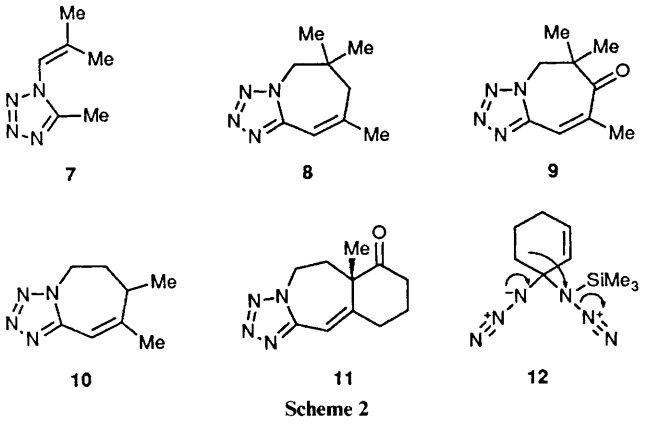
AC =





6 R = $SiMe_2Bu^t$

Scheme 1



Scheme 2

Table 1

Substrate	Reaction time (h)	Yield[a] (%) (adduct)
Mesityl oxide	18	14 (**7**)
Isophorone	22	78 (**8**)
4-Oxoisophorone	48	74 (**9**)
3,4-Dimethylcyclohex-2-enone	10	61 (**10**)
Wieland–Mieschler ketone	18	67 (**11**)

[a] All yields relate to the isolated product after flash column chromatography, except **8** which is after direct crystallisation from absolute ethanol.

reaction with trimethylsilyl azide/trimethylsilyl triflate to destroy the initial product.

A possible explanation for the preferred alkyl migration from the presumed silylated *gem*-diazide intermediate **12** is that it maintains conjugation in the transition state. The highly exothermic loss of dinitrogen should favour a product-like transition state. This simple one-step procedure provides ready access to tetrazole–azepine derivatives.

Experimental

General Procedure.—A solution of the enone (500 mg) in dry dichloromethane (50 cm^3) was stirred at room temperature under argon. To this was added azidotrimethylsilane (3 equiv.) in one portion, followed by trimethylsilyl trifluoromethanesulphonate (3 equiv.) in one portion. The mixture was then stirred at room temperature until TLC indicated complete consumption of the enone. The mixture was quenched with water (50 cm^3), the organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude tetrazole.

5-*Methyl*-1-(2-*methylprop*-1-*enyl*)-1H-*tetrazole* **7**. The crude product (540 mg) was purified by flash column chromatography (silica; ethyl acetate) to give a yellow solid (98 mg, 14%), m.p. 39–40 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3026, 3009, 2952, 2922, 1684, 1619, 1521 and 1447; δ_H(300 MHz; $CDCl_3$) 1.53 and 1.84 (2 × 3 H, s, Me_2C=), 2.34 (3 H, s, N–CMe) and 6.34 (1 H, br s, –CH=); δ_C(75 MHz; $CDCl_3$) 8.72 and 17.89 (C-8 and C-9), 22.45 (=CMe), 114.45 (–CH=C), 141.36 (C=N) and 151.75 (C=CH).

3,3,5-*Trimethyl*-1,8,9,10-*tetraazabicyclo*[5.3.0]*deca*-5,7,9-*triene* **8**. Recrystallisation of the crude product (632 mg) from absolute ethanol afforded pale yellow microneedles (500 mg, 78%), m.p. 116 °C sharp; $\nu_{max}(CHCl_3)/cm^{-1}$ 3013, 2972, 2938, 1669, 1523 and 1460; δ_H(300 MHz; $CDCl_3$) 1.01 (6 H, s, Me_2C), 1.99 (3 H, s, Me–C=), 2.39 (2 H, s, 4-H_2), 4.28 (2 H, s, CH_2–N) and 6.58 (1 H, br s, –CH=); δ_C(75 MHz; $CDCl_3$) 25.91 (2 × *gem*-Me), 27.56 (*Me*–CH=), 31.09 (C-3), 49.15 (C-4), 58.00 (C-2), 108.59 (C-6) and 147.40 (C-7) (Found: M^+, 178.1216. Calc. for $C_9H_{14}N_4$: M^+, 178.1218).

3,3,5-*Trimethyl*-1,8,9,10-*tetraazabicylo*[5.3.0]*deca*-5,7,9-*trien*-4-*one* **9**. Purification of the crude product (720 mg) by flash column chromatography (silica; hexanes-ethyl acetate, 4:1, then 2:1) afforded a pale yellow solid (470 mg, 74%), m.p. 97–99 °C (ethyl acetate) (Found: C, 55.99; H, 6.30; N, 29.44%. Calc. for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3024, 3013, 2935, 1673 and 1460; δ_H(300 MHz; $CDCl_3$) 1.64 (6 H, s, Me_2C), 2.16 (3 H, d, *J* 1.4, *Me*CH=), 4.46 (2 H, s, CH_2–N) and 7.33 (1 H, d, *J* 1.4, CH=); δ_C(75 MHz; $CDCl_3$) 21.37 (Me), 22.43 (2 × *gem*-Me), 45.85 (C-3), 52.66 (C-2), 117.74 (C-6), 142.77 (C-5), 150.41 (C-7) and 200.00 (C=O); *m/z* 192 (M^+) and 137 (100%).

4,5-*Dimethyl*-1,8,9,10-*tetraazabicyclo*[5.3.0]*deca*-5,7,9-*triene* **10**. The crude product (712 mg) was purified by flash column chromatography (silica; hexanes–ethyl acetate, 3:2) to give a yellow wax (410 mg, 62%), m.p. 48–50 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3024, 3007, 1665, 1522 and 1456; δ_H(300 MHz; $CDCl_3$) 1.03 (3 H, d, *J* 8, 4-Me), 1.87 (3 H, s, 5-Me), 1.93 (2 H, m, 2 × 3-H), 2.55 (1 H, m, 4-H), 4.2–4.6 (2 H, m, 2 × 2-H) and 6.25 (1 H, s, –CH=C); δ_C(75 MHz; $CDCl_3$) 18.17 (C-3), 25.42 (*Me*CH), 28.65 (*Me*CH=), 37.54 (MeC*H*), 43.55 (CH_2–N), 107.38 (–CH=C), 150.96 (–*C*=CH) and 154.69 (C=N) (Found: M^+, 164.1061. Calc. for $C_8H_{12}N_4$: M^+, 164.1062).

6a-*Methyl*-6,6a,9,10-*tetrahydro*-5H-*tetrazolo*[5,1-b][3]-*benzazepin*-7(8H)-*one* **11**. The crude product (700 mg) was purified by flash column chromatography (silica; ethyl acetate–hexanes, 1:1 then 2:1) to give a brown–orange solid (410 mg, 67%), m.p. 94–95 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3026, 3020, 3016, 2957, 1714, 1655, 1525 and 1429; δ_H(300 MHz; $CDCl_3$) 1.42 (3 H, s), 1.70 (2 H, m), 2.1–2.9 (6 H, m), 4.48 (2 H, m) and 6.58 (1 H, d, *J* 1.4); δ_C(75 MHz; $CDCl_3$) 23.40 (CH_2), 25.88 (Me), 32.21, 34.59 and 37.04 (all CH_2), 55.88 (quarternary C), 108.76 (CH=), 150.69 (*C*=CH), 154.39 (C=N) and 209.73 (C=O) (Found: M^+, 218.1168. Calc. for $C_{11}H_{14}N_4O$: M^+, 218.1175).

Acknowledgements

The National Institutes of Health are thanked for their support of this research.

References

1 M. D. Lee, T. S. Dunne, M. M. Seigel, C. C. Chang, G. O. Morton and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3464; M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Seigel, G. O. Morton, W. J. McGahren and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3466.

2 J. Golik, G. Dubay, G. Groenewold, M. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3462; J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, M. Ohkuma, K. Saitoh and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3461; M. Konishi, H. Ohkuma, K. Saitoh, H. Kawaguchi, J. Golik, G. Dubay, G. Groenewold, B. Krishnan and T. W. Doyle, *J. Antibiot.*, 1985, **38**, 1605.

3 P. Magnus and P. A. Carter, *J. Am. Chem. Soc.*, 1988, **110**, 1626; P. Magnus, R. T. Lewis and J. C. Huffman, *J. Am. Chem. Soc.*, 1988, **110**, 6921.

4 For references that describe the synthesis of tetrazoles from saturated aldehydes and ketones see: K. Nishiyama and A. Watanabe, *Chem. Lett.*, 1984, 455; K. Nishiyama and T. Yamaguchi, *Synthesis*, 1988, 106; K. Nishiyama and I. Miyata, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2419; K. Nishiyama, M. Oba and A. Watanabe, *Tetrahedron*, 1987, **43**, 693; R. M. Moriarty and K-C. Hou, *Synthesis*, 1984, 683; S. Kirchmeyer, A. Mertens and G. A. Olah, *Synthesis*, 1983, 500.

5 Cholest-4-ene-3,6-dione reacts with sodium azide–boron trifluoride/chloroform to give a ring expanded tetrazole resulting from alkyl migration rather than alkenyl migration: H. Singh, K. K. Bhutani and L. R. Gupta, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1210.
6 For a review of tetrazole chemistry see: R. H. Butler, *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky, C. W. Rees, Pergamon, vol. 5, p. 781, 1984. Pentamethylene tetrazole is a CNS stimulant and narcotic antagonist: K. F. Schmidt, *Ber.*, 1924, **57**, 704.

Paper 1/02792A
Received 10*th June* 1991
Accepted 29*th July* 1991