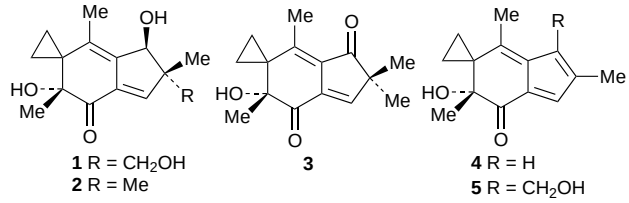
Total synthesis of hydroxymethylacylfulvene, an antitumour derivative of illudin S

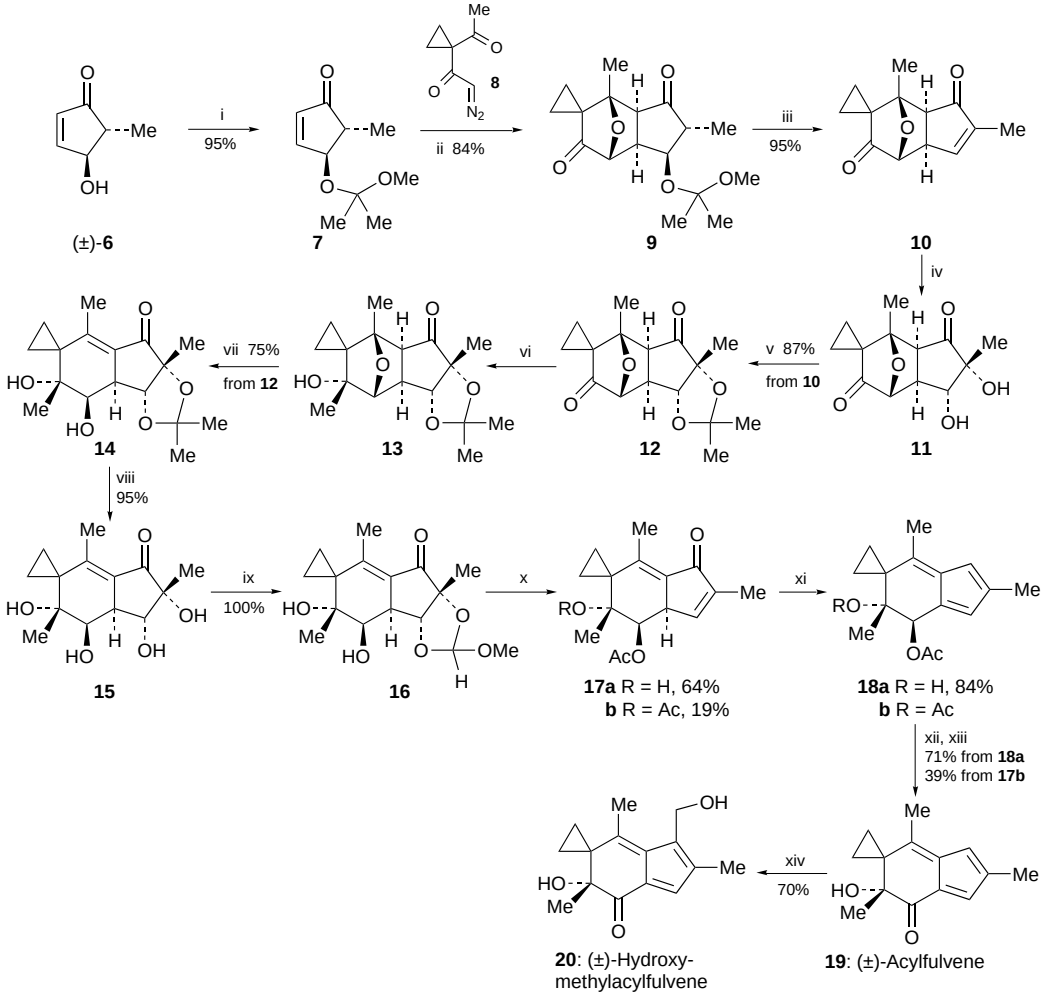
Trevor C. McMorris,*[a] Yi Hu,[a] Jian Yu[a] and Michael J. Kelner[b]

[a] *Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093, USA*
[b] *Department of Pathology, University of California, San Diego, La Jolla, CA 92093, USA*

(±)-Hydroxymethylacylfulvene is synthesized in 14 steps from 4-hydroxy-5-methyl-2-cyclopenten-1-one and 1-acetyl-1-(diazoacetyl)cyclopropane in 15% overall yield.

Acylfulvenes are a new class of potent antitumour compounds derived from the toxic sesquiterpene illudin S **1**.[1,2] The latter and illudin M **2** are produced in cultures of the basidiomycete *Omphalotus illudens*.[3] These two compounds also possess antitumour activity but were found to have poor therapeutic indices when tested *in vivo*, particularly in solid tumour systems. Studies on the mechanism of toxicity of illudins have led to the preparation of illudin derivatives with greatly improved therapeutic indices compared to the parent compounds. Thus first generation analogue dehydroilludin M **3**[4] showed better efficacy against metastatic MV 522 lung carcinoma xenografts (established in 4-week old athymic





Scheme 1 *Reagents and conditions*: i, 2-Methoxypropene, $POCl_3$, room temp., 12 h; ii, $Rh_2(OAc)_4$, CH_2Cl_2, DMF, reflux, 1.5 h; iii, KOH–MeOH, room temp., 1 h; iv, OsO_4, NMO, THF, H_2O, room temp., 24 h; v, dimethoxypropane, *p*-TsOH, MeCN, room temp., 10 h; vi, MeMgCl, THF, −78 °C, 2.5 h; vii, KOH–MeOH, 80 °C, 2 h; viii, Dowex resin, H^+ form, MeOH, room temp., 12 h; ix, $HC(OMe)_3$, *p*-TsOH, room temp., 2 h; x, Ac_2O, reflux, 1.5 h; xi, $CeCl_3·7H_2O$, $NaBH_4$, MeOH–THF (1 : 3), 0 °C to room temp., 5% HCl; xii, $LiAlH_4$, diethyl ether; xiii, Dess–Martin reagent, CH_2Cl_2, room temp., 1 h; xiv, $(CH_2O)_n$, H_2SO_4, H_2O–acetone, room temp., 20 h

Balb/c nu/nu mice) than nine known anticancer agents including cisplatin, cytoxan and paclitaxel. Its efficacy was comparable to that of mitomycin C.[5] The efficacy of second generation analogue acylfulvene **4** exceeded that of dehydroilludin M and mitomycin C.[6] Although these compounds prolonged lifespan in the MV 522 model, they did not induce regression of the primary tumour implants. However, a third generation analogue hydroxymethylacylfulvene (HMAF) **5** caused complete tumour regression in all animals at the maximum tolerated dose of 10 mg Kg^{-1} (iv or ip) three times per week for three weeks. This resulted in an increase in life span of more than 150%.[7] HMAF has also been found to exhibit outstanding activity against breast, colon and skin cancer cell lines derived from human tumours. This compound is now undergoing clinical trials.[8]

HMAF can be prepared readily from acylfulvene **4**, with paraformaldehyde in dilute H_2SO_4 solution in 73% yield, or directly from illudin S. However, the total synthesis of acylfulvenes remains a very desirable objective, because it will make available a variety of analogues for structure–activity investigations. The synthesis of (±)-hydroxymethylacylfulvene has been accomplished as follows.

(±)-4-Hydroxy-5-methylcyclopent-2-enone (±)-**6**†[9] was converted to the acetal **7** (2-methoxypropene, $POCl_3$). The latter and rhodium acetate were added to dichloromethane containing dimethylformamide. A solution of diazoketone **8**[10] in dichloromethane was added slowly to the refluxing solution.[10,11] The intermediate carbonyl ylide underwent a 1,3-dipolar cycloaddition reaction with the cyclopentenone to form the adduct **9** in 84% yield, isolated as one enantiomeric pair. Compound **9** was sensitive to base and was converted in high yield (95%) to cyclopentenone **10** with methanolic KOH at room temperature. Further base treatment of **10**, in an attempt to cleave the oxygen bridge, led to extensive decomposition. Because of the electrophilicity of the cyclopropyl ring and reactivity of the unsaturated ketone, many other efforts also failed to give the desired oxygen bridge-opened compound. The double bond was therefore masked by forming diol **11** with OsO_4, NMO in THF at room temperature. Diol **11** was converted to the acetonide **12** with dimethoxypropane and *p*-TsOH (87% for two steps). Regioselective reaction of **12** with methylmagnesium chloride (THF, −78 °C) afforded the Grignard product **13**. Treatment of **13** with 10% KOH–MeOH at 80 °C for 2 h cleaved the oxygen bridge giving the diol **14** (75% for the two steps). The acetonide was next hydrolysed (Dowex resin, H^+ form, MeOH, 12 h) giving the tetraol **15** (95%).[12] Compound **15** was converted to the orthoester **16** (trimethyl orthoformate, *p*-TsOH, room temp.) and the latter was heated in acetic anhydride (reflux, 1.5 h).[13] A mixture of mono- and di-acetate (**17a** 64%, **17b** 19%) was obtained. Reduction of **17a** with $NaBH_4$, $CeCl_3 \cdot 7H_2O$ in THF and methanol gave an unstable product and the hydroxy group was eliminated on work up yielding the fulvene **18a** (84%). Reduction of the acetate **18a** ($LiAlH_4$, diethyl ether, room temp., 10 min) followed by oxidation of the resulting alcohol with Dess–Martin reagent[14a,b] yielded (±)-acylfulvene **19** (71%) as a yellow gum. Diacetate **17b** could also be converted similarly to **19** (40%). Finally, (±)-hydroxymethylacylfulvene **20** was obtained from **19** following the known procedure.[2]

The spectral properties of (±)-hydroxymethylacylfulvene **20** and (±)-acylfulvene **19** were identical to those of the hydroxymethylacylfulvene and acylfulvene derived from illudin S.

This investigation was supported by MGI Pharma Inc., Minnetonka, Minnesota, USA.

Footnote

† The new compounds **6**–**20** were fully characterised by spectroscopic data including HRMS.

References

1 T. C. McMorris, M. J. Kelner, W. Wang, M. A. Diaz, L. A. Estes and R. Taetle, *Experientia*, 1996, **52**, 75.
2 T. C. McMorris, M. J. Kelner, W. Wang, J. Yu, L. A. Estes and R. Taetle, *J. Nat. Prod.*, 1996, **59**, 896.
3 T. C. McMorris and M. Anchel, *J. Am. Chem. Soc.*, 1965, **87**, 1594.
4 T. C. McMorris, M. J. Kelner, W. Wang, L. A. Estes, M. A. Montoya and R. Taetle, *J. Org. Chem.*, 1992, **57**, 6876.
5 M. J. Kelner, T. C. McMorris and R. Taetle, *Anticancer Res.*, 1995, **15**, 873.
6 M. J. Kelner, T. C. McMorris, L. A. Estes, M. A. Montoya, R. Starr, K. Samson and R. Taetle, *Cancer Res.*, 1995, **55**, 4936.
7 M. J. Kelner, T. C. McMorris, L. A. Estes, W. Wang, K. M. Samson and R. Taetle, *Investigational New Drugs*, 1996, **14**, 161.
8 Unpublished data provided by MGI Pharma Inc., Minneapolis. This company has been licensed by the University of California to develop illudin analogues for treating tumours. U.S. Patents 5,439,936, 5,439,942, 5,523,490 and 5,563,176 on these compounds have been issued to the University of California, and several more are pending.
9 G. Piancatelli, A. Scettri and S. Barbadoro, *Tetrahedron Lett.*, 1976, **39**, 3555.
10 A. Padwa, E. A. Curtis and V. P. Sandanayaka, *J. Org. Chem.*, 1996, **61**, 73.
11 F. R. Kinder and K. W. Bair, *J. Org. Chem.*, 1994, **59**, 6965.
12 M. Kitamura, M. Isobe, Y. Ichikawa and T. Goto, *J. Am. Chem. Soc.*, 1984, **106**, 3252.
13 P. Camps, J. Cardellach, J. Font, R. M. Ortuno and O. Ponsati, *Tetrahedron*, 1982, **38**, 2395.
14 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277; R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.

Received, 17th October 1996; Com. 6/07077I