Tetrahedron Letters,Vol.30,No.18,pp 2333-2336,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CATIONIC CYCLOPENTANNELATION. SYNTHESIS OF (d,l)-XANTHOCIDIN

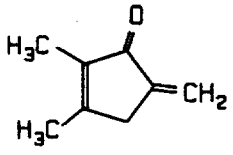
Marcus A. Tius*[1] and Donald P. Astrab

Department of Chemistry, University of Hawaii
Honolulu, Hawaii 96822, U.S.A.

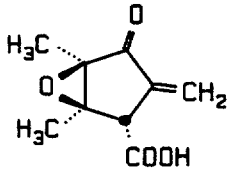
Summary: A cationic cyclopentannelation reaction has been used for the key step of a concise synthesis of (d,l)-xanthocidin. An improvement on our previously described procedure for the preparation of **9** is reported.

A cationic cyclopentannelation reaction which was discovered in our laboratories[2] offers an extremely direct method for the preparation of substituted alpha-methylene cyclopentenones from simple, acyclic precursors. The efficiency of this reaction has been demonstrated with straightforward syntheses of methylenomycin B[3] and (d,l)-methylenomycin A.[4] We now describe a synthesis of (d,l)-xanthocidin,[5] structurally the most complex of the cyclopentane antibiotics.

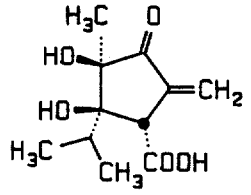
Xanthocidin was isolated from culture filtrates of a Streptomyces in 1966 and was shown to have *in vitro* activity against *E. coli* and *S. aureus*.[5] Structural studies were complicated by the labile nature of the compound, and the relative and absolute stereochemistry remained undefined until 1980 at which time a single crystal X-ray study was published.[6] The total synthesis of (d,l)-xanthocidin was first reported in 1983 by Smith[7] through a very ingenious route, and more recently also by Au-Yeung[8] in 1985.



Methylenomycin B



Methylenomycin A



Xanthocidin

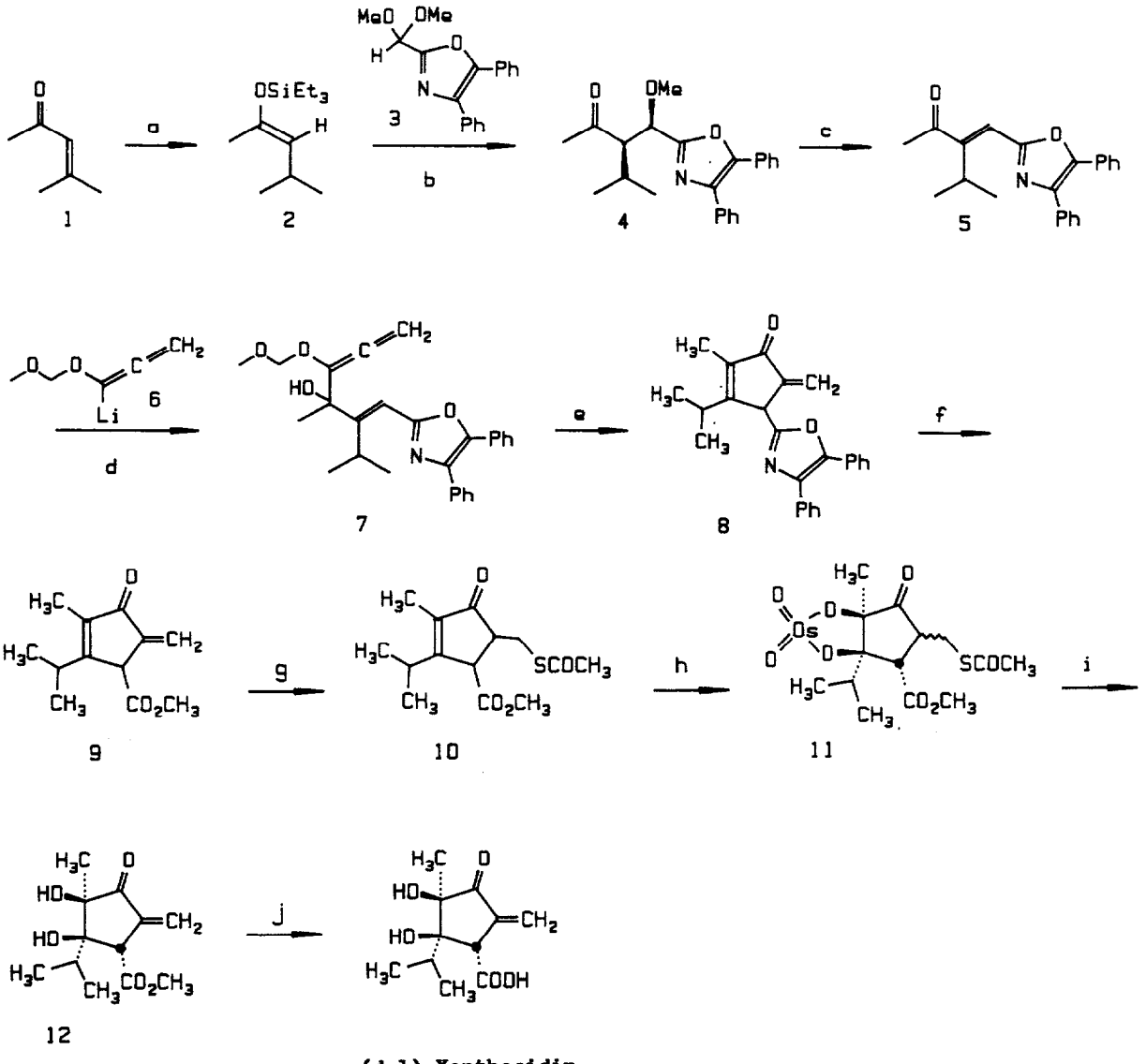
Mesityl oxide **1** was the starting material for our synthesis. Catalytic hydrosilylation[9] with triethylsilane at 40° C in the presence of Wilkinson's catalyst produced *E*-triethylsilyl enol ether **2** in quantitative yield. The condensation of **2** with the 4,5-diphenyloxazole derived dimethyl acetal **3**[10] was mediated by trimethylsilyl trifluoromethanesulfonate at -78° C.[11] The product **4** was isolated in 81% yield as a 10/1 mixture of syn and anti diastereomers. This improvement over our earlier result[3a] was achieved by careful control of the purity of the reagent and solvent. The stereochemistry of the addition was consistent with precedent and has been rationalized by postulating an extended transition state.[11] The diphenyloxazole group served a dual purpose. It served as a photolabile carboxylate intermediate[12] and it also stabilized the cyclization intermediate. Treatment of **4** at 0° C with potassium *tert*-butoxide in THF/*tert*-butanol produced enone **5** in 88% yield as a **single** geometrical isomer. This is

an improvement over our earlier method which used DBU,[3a] since with potassium tert-butoxide, both syn and anti isomers led to a single geometric isomer, trans enone **5**. The addition of the lithio anion **6** of (methoxy)methoxyallene[13] to **5** produced **7**, the substrate for the cationic cyclization reaction, in 86% yield. Control of alkene geometry is crucial for the success of the cyclization reaction. The adduct of **6** with the Z-isomer of **5** failed to undergo cyclization, presumably because the intermediate cation was prevented from achieving planarity, and conrotatory electrocyclization was inhibited. Exposure of **7** to 2,6-lutidine and trifluoroacetic anhydride in dichloromethane at -10° C, followed by gradual warming to 0° C, produced cyclopentenone **8** in 72% yield. The unmasking of the carboxylate function was accomplished by treatment with singlet oxygen (Sensitox, tungsten lamp) in methanol at 25° C, followed by filtration of the reaction mixture through Celite and exposure to a solution powdered potassium carbonate in methanol.[12] Methyl ester **9** was isolated in 71% yield.

The introduction of the cis vicinal hydroxyl groups required the protection of the reactive **exo**-methylene group of **9**. Treatment of **9** with a small excess of thiolacetic acid in the presence of 2,6-lutidine in THF at -10° C, followed by slow warming to 25° C, produced in 83% yield a 4/1 mixture of cis and trans diastereomers. The separation of the diastereomeric mixture by flash column chromatography was straightforward, but was unnecessary: osmylation (OsO_4, pyridine, 25° C, 2-4 h) of each of the diastereomers of **10** took place trans to the methyl carboxylate group. The osmate ester **11** was isolated in 81% yield as a dark solid, which was characterized by ^1H nmr but was not purified. After much effort it was found that the decomposition of **11** to the diol could be accomplished by dissolving the osmate in dry dichloromethane and fitting the flask to a drawn pipette for a hydrogen sulfide inlet. Hydrogen sulfide gas was bubbled through the solution for 2 h at 25° C and the progress of the reaction was monitored by tlc. During the course of the reaction the dark solution gradually cleared with the formation of a dark precipitate, presumed to be osmium salts. Careful removal of the solids by filtration was followed by the immediate treatment of the solution with 0.85 equiv of DBU.[14] After 20 min the reaction mixture was worked up to produce (d,l)-xanthocidin methyl ester **12** in 37% yield as a pale yellow oil.[15] Methyl ester **12**, like xanthocidin, was quite unstable and was prone to undergo spontaneous dehydration even upon storage in frozen benzene at -5° C. Notwithstanding, **12** was converted to (d,l)-xanthocidin by hydrolysis in an ether/1N aqueous NaOH two-phase mixture. The ethereal layer was monitored by tlc for dissappearance of **12**. After 15 min the layers were separated, the aqueous layer was acidified to pH 3 with 10% aqueous HCl, and was extracted twice with dichloromethane. Solvent evaporation produced (d,l)-xanthocidin in 26% yield. This material was identical by spectroscopic comparison (^1H nmr, ir, uv) with the natural material isolated by Asahi,[5] and the synthetic compound prepared by Smith.[7]

The cationic cyclopentannelation reaction has been applied to an eleven-step total synthesis of (d,l)-xanthocidin. The efficiency of this reaction suggests its use for the synthesis of other cyclopentane containing natural products.

Scheme I[a]



(d,l)-Xanthocidin

[a] (a) Et_3SiH, $RhCl(PPh_3)_3$, 40° C; 100%; (b) **3**, TMSOTf, CH_2Cl_2, CH_3CN, -78° C; 81%, 10/1 syn/anti; (c) t-BuOK, t-BuOH, THF, 0° C; 88%; (d) **6**, THF, Et_2O, -78° C; 86%; (e) 2,6-lutidine, TFAA, -10 to 0° C; 72%; (f) i. Sensitox, $^1O_2$, MeOH; ii. K_2CO_3, MeOH; 71%; (g) CH_3COSH, 2,6-lutidine, -10 to 25° C; 83%, 4/1 cis/trans; (h) OsO_4, pyridine, 25° C, 2-4 h; 81%; (i) i. H_2S gas, CH_2Cl_2; ii. DBU, CH_2Cl_2; 37%; (j) i. Et_2O/ aq NaOH, 15-20 min; ii. aq HCl; extract; 26%.

Acknowledgement is made to the National Science Foundation (CHE 86-02328) for their generous support. We thank Professor Amos B. Smith, III, and Dr. Tatsuo Haneishi of Sankyo Co., Ltd., for supplying us with spectra.

References

1. Fellow of the Alfred P. Sloan Foundation, 1987-1988.
2. M. A. Tius and D. P. Astrab, Tetrahedron Lett., 1539-1542 (1984).
3. (a) M. A. Tius, D. P. Astrab, A. H. Fauq, J.-B. Ousset and S. Trehan, J. Am. Chem. Soc., **108**, 3438-3442 (1986); (b) M. A. Tius, G. M. L. Patterson and D. P. Astrab, J. Antibiotics, **38**, 1061-1067 (1985).
4. M. A. Tius and S. Trehan, J. Org. Chem., in press.
5. (a) K. Asahi, J. Nagatsu and S. Suzuki, J. Antibiotics, **A19**, 195-199 (1966); (b) K. Asahi and S. Suzuki, Agric. Biol. Chem., **34**, 325-326 (1970).
6. T. Sakurai, Y. Iimura and K. Asahi, Agric. Biol. Chem., **44**, 2257-2258 (1980).
7. A. B. Smith, III, and D. Boschelli, J. Org. Chem., **48**, 1217-1226 (1983).
8. B.-W. Au-Yeung and Y. Wang, J. Chem. Soc., Chem. Commun., **12**, 825-827 (1985).
9. I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi and K. Nakatsugawa, J. Organomet. Chem., **94**, 449-461 (1975).
10. Dimethyl acetal **3** was prepared from commercially available 2-methyl-4,5-diphenyloxazole in 82% yield by sequential treatment with LDA and trimethyl orthoformate.
11. S. Murata, M. Suzuki and R. Noyori, J. Am. Chem. Soc., **102**, 3248-3249 (1980).
12. H. H. Wasserman and R. J. Gambale, J. Am. Chem. Soc., **107**, 1423-1424 (1985). For a review, see: H. H. Wasserman and B. H. Lipshutz in "Singlet Oxygen": H. H. Wasserman and R. W. Murry, Eds.; Academic Press: New York, 1979; Chapter 9.
13. S. Hoff, L. Brandsma and J. F. Arens, Recl. Trav. Chim. Pays-Bas, **87**, 916-924 (1968).
14. After the completion of this work, a model study showed that the elimination of thiolacetic acid in systems related to **11** could be accomplished in much higher yield by exposure to silver oxide/silver nitrate in ethanol.
15. **12**: tlc Rf=0.36 (50% EtOAc/hexanes); ir (neat) 3420 (br), 2960, 1740, 1708, 1260, 1105, 1023, 1000, 928, 765 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) 6.45 (d, J=2 Hz, 1 H), 5.83 (d, J=2 Hz, 1 H), 5.00 (br s, 2 H), 3.84 (t, J=2 Hz, 1 H), 3.66 (s, 3 H), 2.44 (septet, J=7 Hz, 1 H), 1.47 (s, 3 H), 1.07 (d, J=7 Hz, 3 H), 1.05 (d, J=7 Hz, 3 H) ppm; mass spectrum m/e 242 (M^+, weak), 224 ($M^+ - H_2O$, 100%), 207, 181, 165, 163, 59; exact mass calcd for $C_{12}H_{18}O_5$ 242.1154, found 242.1163; exact mass calcd for $C_{12}H_{16}O_4$ (M^+-H_2O), 224.1049, found 224.1031.

(Received in USA 16 January 1989)