Tetrahedron Letters,Vol.30,No.41,pp 5599-5602,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC DIELS-ALDER REACTIONS: EPC-SYNTHESIS OF A STABLE SARKOMYCIN PRECURSOR (CYCLOSARKOMYCIN)**

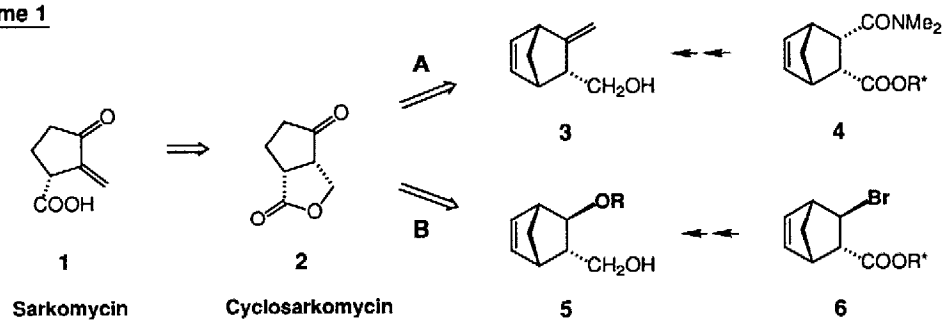
Günter Linz, John Weetman, A.F. Abdel Hady and Günter Helmchen*

Organisch-Chemisches Institut der Universität, Im Neuenheimer Feld 270, D-6900 Heidelberg

Summary: The first synthesis of enantiomerically pure cyclosarkomycin, a stable, crystalline precursor of the antitumor agent sarkomycin is reported. Key steps are an asymmetric Diels-Alder reaction of the (E)-3-bromoacrylate of (R)-pantolactone and introduction of oxygen functionality via elimination/ß-addition. The synthesis of cyclosarkomycin was accomplished in 9 steps [from (E)-3-bromoacrylic acid] in 17 % overall yield.

The antibiotic sarkomycin (1), an antitumor agent, has been a target of numerous synthetic efforts, commonly directed at the racemic compound[1]. Recently, we reported syntheses of both enantiomers of sarkomycin methyl ester, using a strategy based on the retro Diels-Alder reaction[2]. Unfortunately, it was impossible to cleanly characterize or use these compounds, because of their high rate of di- and polymerization[3]. In order to provide a more useful route to sarkomycin we undertook an effort directed at the stable lactone 2, first prepared in racemic form by Marx and Minaskanian[1n], from which the unstable sarkomycin is obtained by treatment with acid.

Scheme 1

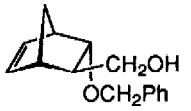


The synthetic strategy is described in Scheme 1. It was our initial plan (route A) to prepare 2 by one-pot oxidative cleavage, lactonisation and decarboxylation of the enantiomerically pure methylenenorbornene 3, which is readily available from the Diels-Alder adduct 4[4]. Despite intense efforts, using a variety of methods (ozonolysis, RuO_4-oxidation), we were unable to accomplish the step 3 – 2. We then turned to the somewhat less ambitious route B which was successful. Route B was inspired by our finding that the

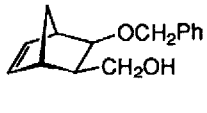
bromo substituent of the Diels-Alder adduct **6**, obtained from the (E)-3-bromoacrylate of (R)-pantolactone and cyclopentadiene, can be replaced by OR upon treatment with alkoxide via elimination and conjugate addition.

Asymmetric Diels-Alder reactions with enoates of (R)-pantolactone (**7**) (commercially available) or (S)-N-methyl-hydroxysuccinimide (**8**) [obtained in one step from (S)-malic acid] can be planned with a considerable degree of confidence[5]. Thus, the (E)-3-bromoacrylates **9** and **10** (Scheme 2) were obtained by acid catalyzed esterification (cat. H_2SO_4, benzene, reflux, 20 h) of (E)-3-bromoacrylic acid[6] with **7** and **8** in 79 %[7] and 63 % yield, respectively[8]. $TiCl_4$-catalyzed DA-reactions with cyclopentadiene proceeded with excellent diastereoselectivity (HPLC analysis) to give crystalline major endo-products which were obtained pure by recrystallization (yields of 78 % and 70 % for **11a**[9] and **11b'**, respectively).

Treatment of the ester **11a** with sodium phenylmethyloxide[10] in THF/DMF 5:1 gave (via elimination, transesterification and conjugate addition) a mixture of stereoisomers consisting mainly of **12** (yield: 88 %, Scheme 3). These compounds were found to slowly deteriorate upon storage and, therefore, the mixture was reduced (LAH) to the stable alcohols **13**. MPLC (silica, petrolether/ethyl acetat 80:20) furnished the major isomer **13a** in 79% yield and the isomers **13b** and **13c** in yields of 11% and 4%, respectively[11].



13b

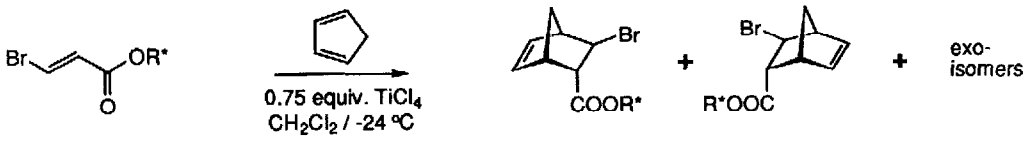


13c

Oxidative cleavage of the double bond of **13a** with ozone under a variety of conditions gave poor results. Excellent results were obtained by transformation of alcohol **13a** to the acetate **14** (Ac_2O, Py, 99 % yield) and oxidation of this with catalytic RuO_4[12] under carefully controlled conditions avoiding over-oxidation to the corresponding benzoate. The crude product was treated with LiOH (THF/H_2O) and the resultant hydroxy acid subjected to mild acid treatment [7 equiv. of HCl (2N), $Et_2O/THF/H_2O$] to give the crystalline lactone **15** (mp 85.5-86 °C) in 71 % yield.

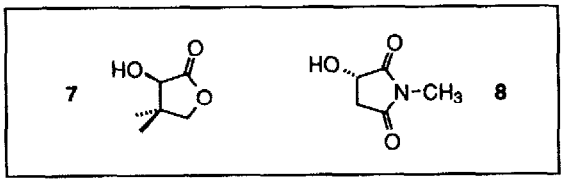
Our initial plan called for debenzylation of **15** followed by oxidation of the resultant hydroxy acid to the ß-keto acid and decarboxylation. Poor results were obtained. However, decarboxylation of **15** according to Barton's method[13] proved to be excellent and gave the lactone **16** (oil) in 73 % yield. Subsequent hydrogenolysis furnished the crystalline alcohol **17** [mp 82.5-83 °C, $[\alpha]_D$ = -102.3 (20 °C, c = 2.02, CH_2Cl_2)] in quantitative yield. Oxidation of **17** with (cat.) $N(n\text{-Prop})_4RuO_4$ according the method of Ley[14] furnished (-)(2S,3R)-cyclosarkomycin (**2**) in 70 % yield. (-)-**2** forms large colourless plates [mp 59.5-60 °C, $[\alpha]_D$ = -397 (20 °C, c = 2.00, CH_2Cl_2)].

Scheme 2

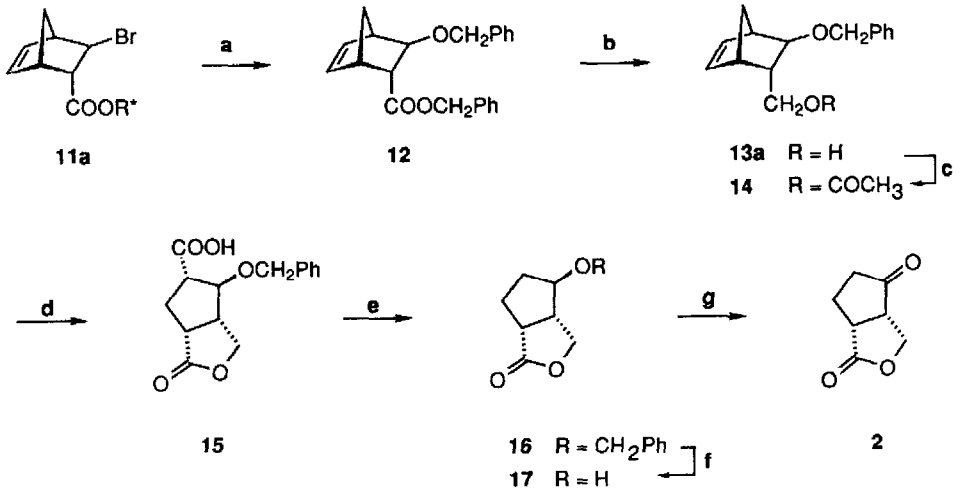


9 R*OH = 7 — endo-exo ratio = 54:1; ratio of **11a:11b** = 98:2 → > 99:1 (2 cryst.) — **11a** — **11b**

10 R*OH = 8 — endo-exo ratio = 38:1; ratio of **11a':11b'** = 2:98 → << 1:99 (2 cryst.) — **11a'** — **11b'**



Scheme 3



(a) 6.0 Equiv. of $NaOCH_2Ph$, THF/DMF 5:1, -10 °C to rt, 17 h; (b) $LiAlH_4$, Et_2O, reflux, 1 h; (c) Ac_2O, Py, 3 h; (d) cat. $RuCl_3/NaIO_4$, $CCl_4/CH_3CN/H_2O$ 1:1:1.5, rt, 3 h; 3.2 equiv. of LiOH, THF/H_2O 5:4, 0 °C, 45 min; 7 equiv. of 2N HCl, Et_2O, 0 °C to rt, 2 h; (e) 1.0 equiv. of N-methylmorpholine, 1.0 equiv. of isobutylchloroformate, THF, -15 °C, 10 min; 1.2 equiv. of N-hydroxy-2-thiopyridone, 1.2 equiv. of NEt_3, THF, -15 °C, 1 h; excess t-butyl mercaptan, irradiation, THF, rt, 2.5 h; (f) H_2, 10% Pd/C, EtOH, 1.5 h; (g) cat. $N(n\text{-Prop})_4RuO_4$, 2.0 equiv. of NMO, MS 4Å, CH_2Cl_2, 20 h, rt.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

1. (a) J. Otera, Y. Niibo, H. Aikawa, Tetrahedron Lett. **1987**, 2147; (b) B. Auyeung, J. Xu, J. Qiu, Huaxue Xuebao, Acta Chimica Sinica **44**, 479 (1986); (c) T. Cohen, Z. Kosarych, K. Suzuki, L.-C. Yu, J.Org.Chem. **50**, 2965 (1985); (d) R. Baker, R.B. Keen, M.D. Morris, R.W. Turner, J.Chem.Soc. Chem.Commun. **1984**, 987; (e) P.G. Baraldi, A. Barco, S. Benetti, G.P. Pollini, E. Polo, D. Simoni, ibid. **1984**, 1049; (f) A. Misumi, K. Furuta, H. Yamamoto, Tetrahedron Lett. **1984**, 671; (g) M. Kodpinid, T. Siwapinyoyos, Y. Thebtaranonth, J.Am.Chem.Soc. **106**, 4862 (1984); (h) J. Froissant, F. Huet, J.-M. Conia, Nouv.J.Chim. **7**, 599 (1983); (i) A.T. Hewson, D.T. MacPherson, Tetrahedron Lett. **1983**, 647; (j) S.V. Govindan, T. Hudlicky, F.J. Koszyk, J.Org.Chem. **48**, 3581 (1983); (k) A.P. Kozikowski, P.D. Stein, J.Am.Chem.Soc. **104**, 4023 (1982); (l) E.J. Barreiro, Tetrahedron Lett. **1982**, 3605; (m) B.A. Wexler, B.H. Toder, G. Minaskanian, A.B. Smith III, J.Org.Chem. **47**, 3333 (1982); (n) J.N. Marx, G. Minaskanian, ibid. 3306 (1982); (o) Y. Kobayashi, J. Tsuji, Tetrahedron Lett. **1981**, 4295; (p) R.K. Boeckmann, P.C. Naegely, S.D. Arthur, J.Org.Chem. **45**, 752 (1980);

2. G. Helmchen, K. Ihrig, H. Schindler, Tetrahedron Lett. **1987**, 183.

3. (a) K. Maeda, S. Kondo, J. Antibiotics **11A**, 37 (1958); (b) T. Hara, Y. Yamada, E. Akita, J. Antibiotics **10A**, 70 (1957).

4. With (R)-pantolactone as auxiliary (R^*OH = 7), diastereomerically pure (2R,3S)-**4** is obtained from the reaction of the corresponding maleate with cyclopentadiene and $MgBr_2 \cdot Et_2O$ as catalyst, and recrystallization. The complementary (2S,3R)-diastereomer is available with Et_2AlCl as catalyst.

5. (a) G. Helmchen, A.F. Abdel Hady, H. Hartmann, R. Karge, A. Krotz, K. Sartor, M. Urmann, Pure Appl.Chem. **61**, 409 (1989); (b) T. Poll, A.F. Abdel Hady, R. Karge, G. Linz, J. Weetman, G. Helmchen, Tetrahedron Lett., preceeding paper.

6. (a) K. Alder, F. Brochhagen, C. Kaiser, W. Roth, Liebigs Ann.Chem. **593**, 1 (1955); (b) G. Just, R. Quellet, Can.J.Chem. **54**, 2925 (1976).

7. The ester **9** was also prepared in 80-85 % yield by esterification of (E)-3-bromoacrylic acid with (R)-pantolactone according to the DCC/DMAP-method; B. Neises, W. Steglich, Angew.Chem. **90**, 556 (1978).

8. All new compounds described herein gave correct elemental analyses and spectra.

9. The absolute configuration of **11a** was determined by transformation (treatment with LiOH in THF/H_2O followed by esterification with diazomethane) to (+)-2-methoxycarbonylnorbornadiene of known absolute configuration: O. De Lucchi, V. Lucchini, C. Marchioro, G. Valle, G. Modena, J.Org.Chem. 51, 1457 (1986).

10. Elimination of HBr is probably the first step. This is inferred from the observation that mild saponification of the adduct **11a** (LiOH, THF/H_2O) yields norbornadiene-2-carboxylic acid. This useful chiral synthon is obtained in 87 % yield as crystals which slowly deterioate upon storage.

11. For large scale work, it may be more convenient to postpone the separation step by subjecting the mixture of isomers **13a-c** to acylation and oxidative double bond cleavage to give a mixture of three dicarboxylic acids of which only one can form a lactone, **15**, upon treatment with acid.

12. P.H.J. Carlsen, T. Katsuki, V.S. Martin, K.B. Sharpless, J. Org.Chem. **46**, 3936 (1981); the rate of oxidation was enhanced dramatically by using $RuCl_3$ instead of RuO_2.

13. D.H.R. Barton, S.Z. Zard, Pure Appl.Chem. **58**, 675 (1986).

14. W.P. Griffith, S.V. Ley, G.P. Whitcombe, A.D. White, J.Chem.Soc. Chem.Commun. **1987**, 1625.

(Received in Germany 17 August 1989)