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ENANTIOMERICALLY HOMOGENEOUS INTERMEDIATES TOWARD THE SYNTHESIS OF DESCARBAMOYLCALICHEAMICINONE

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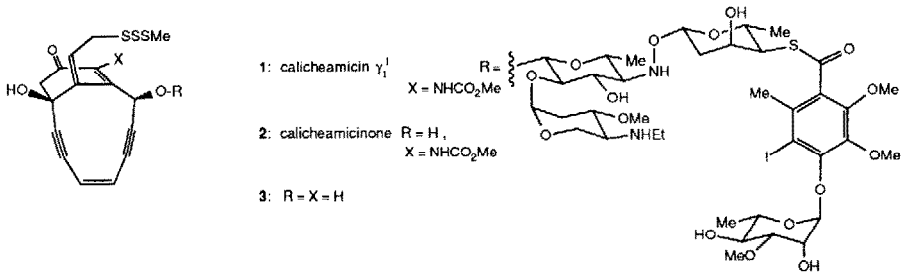
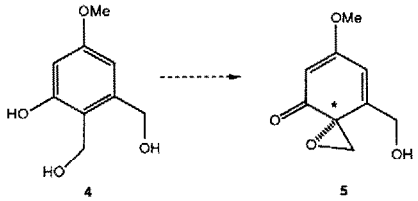
Abstract. Enzymatically mediated kinetic resolution of racemic **12** with lipase PS-30 provides a practical route to the aglycones of descarbamoylcalicheamicin.

Recently we described the total synthesis of racemic calicheamicinone (**2**) the aglycone of the sequence selective DNA cutting drug calicheamicin (**1**).[1] The strategy and many of the experimental designs, which led to **2** were first developed during the course of synthesizing its descarbamoyl congener **3**. Subsequent studies have revealed that **3** retains the powerful cleaving properties exhibited by **2**, albeit in somewhat reduced form.[2] The study described below was directed toward obtaining **2** and **3** in substantially enantiomerically pure form, corresponding in absolute configuration to the aglycone section of **1**. We first attempted to achieve an enantiospecific conversion of phenol **4** to dienone **5** as a route to intermediates *en route* to **3**. While the possibilities for achieving this goal were by no means exhausted, early attempts were not rewarding.

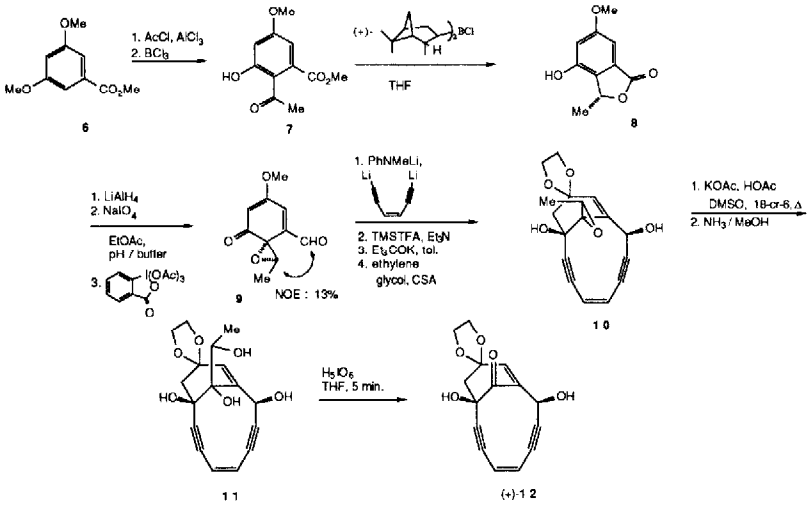




4 5

Instead we focussed on the possibility of building a chiral substrate for a Becker-Adler oxidation.[3] If the Becker-Adler reaction would be stereospecific,[4] the chirality of the spiroepoxide center α- to the carbonyl group would be defined. It is this center which controls the stereochemistry[5] of the enediyne annulation leading to the core (cf **10**). For this purpose, we evaluated the possibility of **8** which we hoped might be obtained via enantiospecific reduction of **7**.[6]

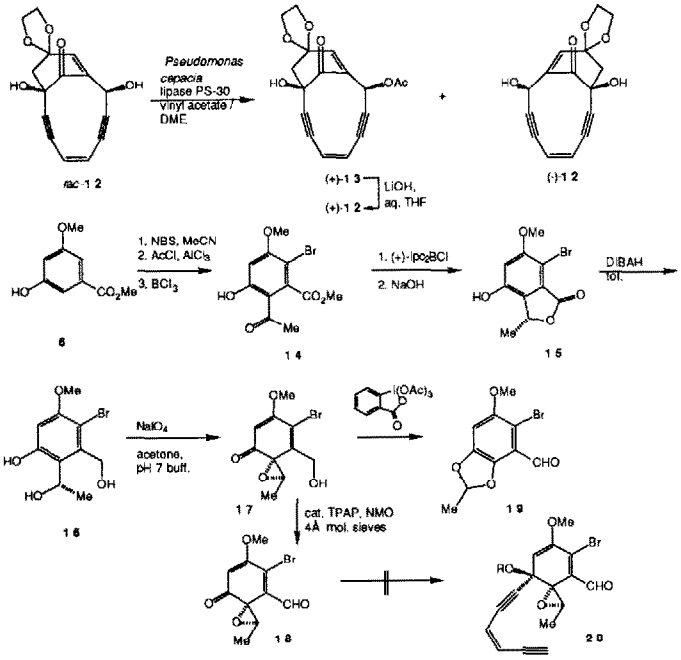
In the event, reduction of **7** with (+)-Ipc_2 BCl under protocols developed by Brown[7] provided a 73% yield of lactone **8**.[8] Reduction of the latter with $LiAlH_4$ followed by Becker-Adler oxidation of the resultant diol with $NaIO_4$, and, thence, by Dess-Martin[9] oxidation gave aldehyde **9** (34% overall) The Becker-Adler reaction is apparently stereospecific. An NOE enhancement (13%) between the "epoxymethine" and aldehydo protons defines the stereochemistry to be as shown. The spirodienone system **9**, containing the additional methyl group, proved to be less stable (*vide infra*) and less amenable to subsequent development than was the case with **5**. After following procedures developed in connection with **5**,[6] **9** was converted to **10** though only in ca. 5% overall yield. Solvolysis of **10** with KOAc-AcOH followed by ammonolysis afforded **11**[8] which underwent smooth cleavage with H_5IO_6 to afford the known **12**.[10] Although the overall route was not viable from the standpoint of synthesis, in conjunction with the Brown work,[7] it served as a basis to assign the absolute configuration of the antipode **12** and *ent* **12** (*vide infra*).[11]



Fortunately a practical solution to the preparative problem was accomplished. Thus treatment of racemic **12** (i.e. *rac* **12**) with vinyl acetate[12] under mediation by lipase PS-30 derived from *Pseudomonas cepacia*[13] resulted in highly selective acetylation of the enantiomer corresponding to the natural series. There was thus obtained a 44% yield of acetate **13** as well as a 47% yield of "unreacted" *ent*-**12**. Hydrolysis of **13** with lithium hydroxide in THF afforded **12** as demonstrated by polarimetric comparisons,[14] and by the identity of its Mosher ester[15] with that derived from **12**.

Attempts to extend the methodology of the enantiospecific synthesis of **12** to the series required for the synthesis of the fully functionalized calicheamicinone started on a favorable note. Reaction of **14**, with (+)-Ipc_2 BCl, prepared from **6** as shown, followed by treatment with sodium hydroxide afforded lactone **15** (>95% ee by Mosher ester analysis). This compound was converted to **16** by reduction with DIBAH followed by

oxidation with sodium metaperiodate to provide **17**. Serious difficulties were encountered in converting **17** to **18** by Dess Martin oxidation. In our hands, this oxidation invariably produced **19** as the major product.[16] The desired **18** could be obtained in low yield by TPAP[17] oxidation of **17**. However, this compound proved to be unstable to attempted purification. A few attempts to convert it to **20** were unrewarding. A solution to the synthesis of enantiomerically pure intermediates *en route* to calicheamicinone is described in the next Letter.



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References

1. Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850.
2. Jacqueline Drak, Ph.D. Thesis, Yale University, **1991**.
3. Adler, E.; Brasen, S.; Miyake, H. *Acta Chem. Scand.* **1971**, *25*, 2055. (b) Becker, H.-D.; Bremholt, T.; Adler, E. *Tetrahedron Lett.* **1972**, 4205.

4. For Becker-Adler rearrangement of a phenyl-substituted system, where the stereochemical outcome is not addressed, see ref. 16.
5. Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Schulte, G. K. *J. Am. Chem. Soc.* **1988**, *110*, 6890.
6. For Friedel-Crafts reactions of **6**, see: Gourmelon, C.; Graff, Y. *Bull. Soc. Chim. Fr.* **1971**, 4032.
7. Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
8. All new compounds were characterized and gave satisfactory ^{1}H NMR, IR and MS. Enantiomeric excess (ee) was determined by ^{1}H NMR analysis of the derived Mosher ester.
9. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
10. Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781.
11. Predicted to reduce from the pro-(*R*) face. See ref. 7.
12. Hsu, S.-H.; Wu, S.-S.; Wang, X.-F.; Wong, C. H. *Tetrahedron Lett.* **1990**, *31*, 6403. (b) Wang, Y.-F.; Chen, S.-T.; Liu, K. K.-C.; Wong, C.-H. *ibid.* **1989**, *30*, 1917. (c) Wang, X.-F.; Wong, C. H. *J. Org. Chem.* **1988**, *53*, 3129. (d) Sweers, H. M.; Wong, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 6421.
13. *Pseudomonas cepacia* lipase PS-30 is commercially available from Amano Int. Enzyme Co., Inc.
14. (+)-12: $[\alpha]_D^{22}$ = +380.3° (*c* 0.3, $CHCl_3$). (-)-12: $[\alpha]_D^{22}$ = -386.0° (*c* 0.4, $CHCl_3$).
15. Dale, J. A.; Dull, D. L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.
16. For a similar oxidative rearrangement see: Becker, H.-D.; Bremholt, T. *Tetrahedron Lett.* **1973**, 197.
17. Griffith, W. P.; Ley, S. V.; Whitcomb, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625.

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