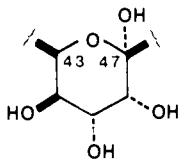
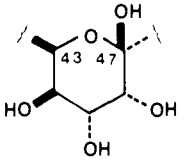
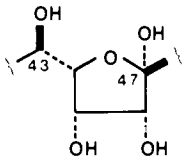


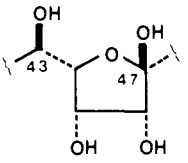
1A-a



1A-b



1B-a



1B-b

warranted here. The misassignment of a large number of stereocenters through primary dependence on NMR methods alone points out the limitation of these types of experiments and the continuing importance of organic synthesis in structure elucidation.

Acknowledgment. Financial assistance from the National Institutes of Health (NS-12108) and the National Science Foundation (CHE 78-06296) to the Harvard group is gratefully acknowledged. The Nagoya group is grateful to the Foundation for the Promotion of Research on Medical Resources and the Ministry of Education, Japanese Government (Grants-in-Aid 411704 and 56540320), for financial support. Appreciation is also expressed for the use of the 500-MHz NMR instrument at the NMR Facility for Biomolecular Research located at the F. Bitter National Magnet Laboratory, MIT. The NMR facility is supported by Grant RR00995 from the Division of Research Resources of the NIH and by the National Science Foundation under Contract C-670.

Practical Asymmetric Synthesis of Aklavinone

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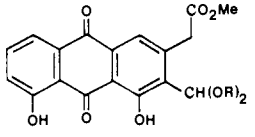
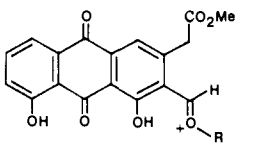
Received August 2, 1982

We recently reported a practical total synthesis of racemic aklavinone (**1**, Chart I), the aglycone of the aclacinomycin group of medicinally important anthracycline antitumor antibiotics.[1-3] One of the key steps of our synthesis involved a crossed aldol reaction of dimethylacetal **2** with $CH_3CH_2COCH_2Si(CH_3)_3$ in



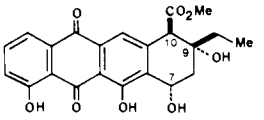
2 : R = Me



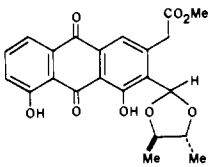
A

CH_2Cl_2 containing $SnCl_4$ at −40 °C. The aldol product was then converted to racemic aklavinone in two steps. In this communication we report a practical synthetic route to optically active aklavinone, utilizing an efficient asymmetric crossed aldol reaction.

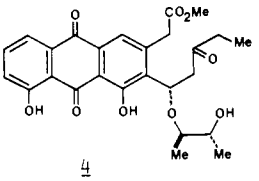
Chart I



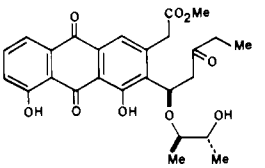
1 : aklavinone



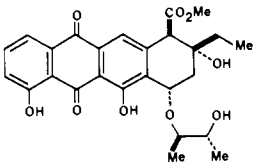
3



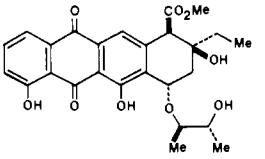
4



5



6



7

It occurred to us that a slight modification of our original synthesis might provide a route to optically active aklavinone.[4] Namely, the acetal corresponding to **2** would allow for generation of chiral oxonium ion A, when the acetal is prepared from an optically active alcohol. The oxonium ion A could, in turn, react with the nucleophile derived from $CH_3CH_2COCH_2Si(CH_3)_3$ from either of its two diastereotopic faces, thereby producing potentially unequal amounts of the two possible diastereomeric aldols.

In order to test this possibility, we synthesized the acetal **3**[5] [mp 192–194 °C; α_D −47.9° (*c* 0.19, $CHCl_3$)] from one of the intermediates used in our previous synthesis.[6] Although **3** was recovered unchanged under the original conditions ($CH_3CH_2COCH_2Si(CH_3)_3/SnCl_4/CH_2Cl_2$/−40 °C),[7] it reacted smoothly and cleanly with $CH_3CH_2COCH_2Si(CH_3)_3$ in *CH_3CN* ($SnCl_4/CH_3CN$/−20 °C/4 h) to yield a 10:1 mixture of the two possible crossed aldol products **4** [mp 120–124 °C; α_D −155° (*c* 0.19, $CHCl_3$)] and **5** [mp 77–86 °C; α_D −14.2° (*c* 0.45, $CHCl_3$)] in 83% combined yield.[8] It is worth noting that the acetal prepared from l-menthol, i.e., R = l-menthol in **2**, gave lower asymmetric induction (product ratio = 1.5:1.0) on crossed aldol reaction.[9]

The absolute configuration at C7 of **4** was concluded from its successful conversion to natural aklavinone (**1**). Namely, treatment of **4** with excess K_2CO_3 in CH_3OH at room temperature for 2 h led to the cyclized products **6** [mp 116 °C and 163–165

†National Institutes of Health Trainee at Harvard University, 1979–1982.

(1) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248.

(2) For the synthesis of aklavinone from other groups, see: (a) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. (b) Confalone, P. N.; Pizzolato, G. *Ibid.* **1981**, *103*, 4251. (c) Li, T.-t.; Wu, Y. L. *Ibid.* **1981**, *103*, 7007.

(3) For recent reviews on the chemistry of anthracycline antibiotics, see references given in ref 1, and the following: Arcamone, F. "Doxorubicin"; Academic Press: New York, 1981.

(4) Kende's synthesis provided optically enriched aklavinone. See the paper quoted under ref 2a.

(5) Satisfactory spectroscopic data were obtained for all new compounds in this paper.

(6) The acetal **3** was synthesized in 92% yield by acetalization [D(−)-2,3-butanediol/*p*-TSA·py/C_6H_6/reflux] of the aldehyde reported as compound **7** in the paper quoted in ref 1. We are indebted to Dr. N. Cohen, Hoffmann-La Roche, Inc., for a generous gift of D(−)-2,3-butanediol.

(7) Under more forcing conditions ($CH_3CH_2COCH_2Si(CH_3)_3/SnCl_4/CH_2Cl_2$/−20 °C → room temperature), **3** did disappear, but many products were observed.

(8) Diastereomers **4** and **5** were easily separated by preparative eluant; gel thin-layer chromatography (12% EtOAc/C_6H_6 as eluant; R_f(**4**) 0.36; R_f(**5**) 0.27).

(9) For use of an optically active acetal derived from D(−)-2,3-butanediol in asymmetric polyene cyclizations, see: Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188.

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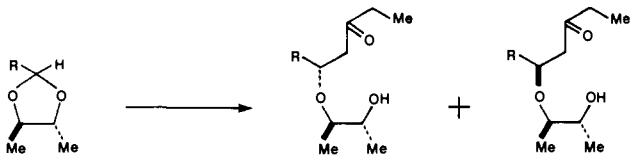
Table I



8 9 10

substance	conditions	products[14,15]
8a, R = C_6H_5	$MeCH_2COCH_2Si(CH_3)_3$/ $SnCl_4$/MeCN/−40 °C	9a-10a (16:1)
8a, R = C_6H_5	CH_2=$CHCH_2Si(CH_3)_3$/ $SnCl_4$/MeCN/−15 °C	9a'-10a' (5:1)
8b, R = $Me(CH_2)_8$	$MeCH_2COCH_2Si(CH_3)_3$/ $SnCl_4$/MeCN/−40 °C	9b-10b (3.1:1)
8c, R = $(Me)_2C$=CH	same	9c-10c (2.3:1)
8d, R = $(Me)_2CH$	same	9d-10d (ca. 1:1)

°C (double melting points); α_D +202° (*c* 0.38, $CHCl_3$)] and **7** [mp 178–180 °C; α_D +180° (*c* 0.15, $CHCl_3$)] in a ratio of 1.3:1.0[10] in 95% combined yield. Acidic hydrolysis of **6** (TFA/−78 °C → room temperature),[11] followed by chromatographic purification, afforded optically active aklavinone [**1**; mp 170–172 °C; α_D +150° (*c* 0.21 $CHCl_3$)][12] in 84% yield. Thus, by utilization of this asymmetric crossed aldol reaction, our synthetic route now provides optically active natural[13] aklavinone in 23% overall yield in six steps from bromojuglone.

Encouraged by the successful asymmetric transformation of **3** to **4**, we subjected four additional acetals, **8a–d** to the crossed aldol reaction (Table I). The absolute configuration of major aldol products **9a**, **9a'**, and **9b** were established by correlating them with known substances.[14] It is worth noting that optically active β-hydroxy ketones were easily obtained from the major aldol products in about 70% overall yield in three steps, i.e., (1) Swern or PCC oxidation, (2) Baeyer–Villiger oxidation (MCPBA/CH_2Cl_2/room temperature), and (3) methanolysis (*p*-TSA·py/CH_3OH/60 °C). As this procedure seems to have good potential for solving other synthetic problems, we are currently engaged in further developments of this reaction.

Acknowledgment. Financial support from the National Cancer Institute (Grant CA 22215) is gratefully acknowledged.

Supplementary Material Available: Experimental details and ^1H NMR spectra (13 pages). Ordering information is given on any current masthead page.

(10) Note that the ratio of **4** to **5** was improved compared with that of the corresponding two diastereomers in the racemic series; however, recycling of **7** was not applicable for the optically active series.

(11) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825.

(12) The absolute configuration of natural aklavinone is as shown in structure **1**. The specific rotation of natural aklavinone was found to be +151° in $CHCl_3$. An authentic sample of aklavinone was prepared by hydrolysis of natural aclacinomycin A. We are indebted to Professor Umezawa, Institute of Microbial Chemistry, and Dr. Oki, Sanraku-Ocean, Inc., for a generous gift of a sample of aclacinomycin A. We thank Dr. M. R. Uskokovic, Hoffmann-La Roche, Inc., for a generous gift of aklavinone, isolated from fermentation broths.

(13) If desired, this synthetic route is applicable for synthesis of the antipode of natural aklavinone by using L(+)- instead of D(−)-2,3-butanediol.

(14) The absolute configuration of **9a'** was established by its successful conversion to known (*S*)-(−)-*n*-PrCH(OH)Ph (Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870) in four steps: (1) H_2/Pd–Pb–$CaCO_3$; (2) PCC oxidation; (3) MCPBA; (4) *p*-TSA·py/MeOH. Aldol product **9a'** was correlated with the PCC oxidation product of **9a** in three steps: (1) O_3; (2) EtMgBr; (3) PCC oxidation, establishing the absolute configuration of **9a**. According to the procedure given in the text, the β-hydroxy ketone was prepared from **9b**, which was then treated with (1) 3,5-$(NO_2)_2C_6H_3CO_3H$, (2) $LiAlH_4$, and (3) Ac_2O/py, to yield (*R*)-(−)-$Me(CH_2)_8CH(OAc)$-CH_2CH_2OAc. An authentic sample was prepared by using Sharpless' asymmetric epoxidation (Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974) and Red-Al reduction of the resultant epoxide (Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719), followed by acetylation.

(15) Compounds **9a'** and **10a'** have a CH_2=$CHCH_2$– group instead of a $MeCH_2COCH_2$– in the structure shown in Table I.

Practical Asymmetric Syntheses of 11-Deoxydaunomycinone and Related Compounds

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Received August 2, 1982

In the preceding paper we reported a practical synthesis of optically active aklavinone using an asymmetric crossed aldol reaction.[1] Encouraged by this success, we explored the possibility of extending our approach to asymmetric syntheses of daunomycinone, adriamycinone, and related compounds. Modification of the functional groups at the C10, C11 and C13 positions are required to realize this plan (cf. the structures in Table I). In this communication we describe a solution that achieves the required functionalization at C10 and C13 and also present a practical asymmetric synthesis of the aglycones of recently discovered 11-deoxydaunomycinone and related anthracycline antibiotics (Table I).[2-6]

The synthesis of **10** demonstrates a general method for modifying the C10 functional group. Analogous to our synthesis of aklavinone,[7] benzofuran **5a** (mp 168–169 °C, Chart I)[8] was synthesized in 70–75% yield from bromojuglone (**3**)[7] and furandiene **4**[9] ($SrCO_3$/radical scavenger/C_6H_6/reflux, followed by air oxidation in $CHCl_3$ containing *i*-Pr_2EtN). Ozonolysis of **5a**, followed by acetalization [L(+)-2,3-butanediol[10]/*p*-TSA·py/toluene/reflux/4 h] gave acetal **6** [mp 121–122 °C; α_D +49° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] in 80–85% yield. Asymmetric aldol reaction of **6** with excess $CH_3CH_2COCH_2Si(CH_3)_3$ (3.0 equiv $SnCl_4/CH_3CN$/−20 °C/2 h) produced an approximately 17:1 mixture of two products, which were separated by using silica gel chromatography to yield **7** [85–90% yield; mp 81–83 °C; α_D +63° (*c* 0.10, 1:1 $CHCl_3/CH_3OH$)] and its C7 epimer (~5% yield).

During the aklavinone synthesis, we noticed that base-induced cyclization of a keto methyl ester similar to **7** in aprotic solvents yielded exclusively a product with the same relative stereochemistry

†National Institutes of Health Trainee at Harvard University, 1979–1982.

(1) McNamara, J. M.; Kishi, Y., *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For recent reviews on the chemistry of anthracycline antibiotics, see ref 3 of the preceding paper.

(3) For asymmetric syntheses of daunomycinone, see: (a) Terashima, S.; Jew, S.-s.; Koga, K. *Tetrahedron Lett.* **1978**, 4937; *Chem. Pharm. Bull. (Tokyo)* **1979**, *27*, 2351. (b) Terashima, S.; Tanno, N.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2753.

(4) For syntheses of 11-deoxydaunomycinone and related compounds, see: (a) Gesson, J.-P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 3351. (b) Bauman, J. G.; Barber, R. B.; Gless, R. D.; Rapoport, H. *Ibid.* **1980**, *21*, 4777. (c) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 576. (d) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (e) Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, *22*, 811. (f) Kende, A. S.; Rizzi, J. P. *Ibid.* **1981**, *22*, 1779. (g) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799. (h) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, *22*, 3711. (i) Gesson, J.-P.; Mondon, M. *J. Chem. Soc., Chem. Commun.* **1982**, 421. (j) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1982**, *23*, 775. (k) Rao, A. V. R.; Mehendale, A. R.; Reddy, K. B. *Ibid.* **1982**, *23*, 2415.

(5) Arcamone, F.; Cassinelli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462.

(6) Cassinelli, G.; Rivola, G.; Ruggieri, D.; Arcamone, F.; Grein, A.; Merli, S.; Spalla, C.; Casazza, A. M.; DiMarco, A.; Pratesi, G. *J. Antibiot.* **1982**, *35*, 176.

(7) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248.

(8) Satisfactory spectroscopic data were obtained for all new compounds in this paper.

(9) An approximately 3:1 mixture of deconjugated and conjugated esters was prepared from 3-furanyl methyl ketone in two steps: (1) $(EtO)_2P(O)$-$CH_2CO_2CH_2CH_2Si(CH_3)_3$/NaH/THF/50 °C; (2) LDA/THF/−78 °C, followed by quenching with phenol. The Diels–Alder reaction was carried out by using 2.7 equiv of the mixture.

(10) This substance was prepared from L(+)-tartaric acid in five steps: (1) $MeC(OMe)_2Me$/MeOH/*p*-TSA/cyclohexane/Δ (Carmack, M.; Kelley, C. J. *J. Org. Chem.* **1968**, *33*, 2171); (2) $LiAlH_4/Et_2O$/room temperature; (3) TsCl/py/0 °C; (4) EtOH/*p*-TSA/Δ; (5) $LiAlH_4/Et_2O$/Δ. We thank Professor Still, Columbia University, for the procedure of steps 2–5.

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