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CHIRAL PROSTANOID INTERMEDIATES FROM AUCUBIN

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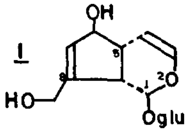
Summary: Several potentially useful prostanoid intermediates have been prepared from aucubin. Dry DMSO-NBS converts enol ethers to α-bromoesters in one step.

Ohno and coworkers quite recently reported[1] their ingenious conversion of aucubin (1) to (+)-11 - deoxy-11α-hydroxymethyl prostaglandin $F_{2\alpha}$ (2)[1-4]. As we have been pursuing an alternate path[5] to the same goal, we would like to report our progress. Our primary target is the homolog (3) of the well-known Corey lactone-aldehyde, and the work is summarized in Scheme I.

1



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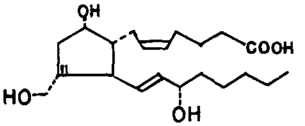

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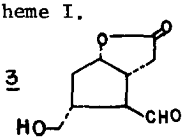

Schmid[6] devised a four step procedure for the conversion of aucubin(1) to lactone-hexa-acetate 7. This involved 1) acetylation to 4, 2) conversion to bromohydrin (bromohemiacetal) 5 (mp 151°C) with Br_2-H_2O/THF, 3) oxidation (CrO_3/HOAc) to bromolactone 6 (mp 166°), and 4) reduction (Zn/HOAc) to lactone 7 (mp 175°)[6]. In our hands, steps 2 and 3 gave poor yields (35 and 50% respectively).

To improve step 2 we tried Dalton's procedure (NBS-H_2O/DMSO)[7], which converted 4 to a mixture of three bromohydrins (Hplc showed 8, 3 parts and 9a+9b, 1 part : total yield 95%), from which 8 (mp 136°) crystallized in 65% yield. Jones oxidation of 8 gave an excellent yield of the same bromolactone obtained previously from 5 (proving thereby that 5 and 8 are hydroxyl epimers).

Bromohydrins 9a and 9b proved to be inseparable, and therefore the crude mother liquors remaining after separation of 8 were oxidized (Jones) directly, affording an excellent yield of a second bromolactone, 10 (mp 123°) (proving therby that 9a and 9b are also hydroxyl epimers).

Both bromolactones 6 and 10 were reduced by Zn/HOAc to lactone 7 (proving thereby that they are bromine epimers).

We subsequently discovered that the use of dry DMSO (distilled from CaH_2) with NBS gave, in 90% yield, a mixture of bromolactones 6 and 10 (3:1, resp.) directly from 4[8]. (Direct reduction of this mixture gave 7 in 90% yield.) Application of this new reaction to dihydropyran gave α-bromo-δ-valerolactone (62%); cyclohexene gave α-bromocyclohexanone (63%).

Hydrogenation of 7 over PtO_2 or Pd/C in EtOAc, EtOH, HOAc, dioxane or water (or mixtures), at -25 to 25°C and 1 to 100 atm., gave mainly products with extensive hydrogenolysis of the allylic acetate groups. On the other hand, hydrogenation of 7 over 5% Rh/C, in EtOAc at 4 atm., gave a 1:1 mixture of 11 and 12 (95% total). At 1 atm., 11 and 12 were formed in a 1:4 ratio (95%), and pure 12 crystallized directly from the reaction mixture in over 75% yield.

Methanolysis of epimer 12 gave only lactol 15 (82%) (with no trace of aldehyde 16 evident by nmr). On the other hand, 11 gave a mixture of lactol 14 (28%) and aldehyde 13 (50%), separated by preparative HPLC. In order to determine the relative orientation of the hydroxymethyl side chain, lactols 14 and 15 were oxidized (Jones), respectively, to keto-lactones 17 (20%)[10] and 18 (95%). The structures of 17 and 18 were confirmed by X-ray analysis, kindly performed by Dr. John Blount (Hoffmann-LaRoche). The absolute stereochemistry of these compounds is inferred from that of aucubin[11], and is the same (at iridoid C-5) as that of the prostanoids (at prostanoid C-8).

Aucubin was isolated from Aucuba japonica[12] by the procedure of Duff[13]: hot water extraction, concentration in vac, and partition chromatography on Celite with water-saturated n-butanol. We have easily accumulated over 500 g. of aucubin by this method (1% of fresh plant weight).

At present we are attempting the conversion of 13 to 3 by inversion of the secondary hydroxyl group and subsequent lactone ring closure. A similar sequence applied to 15 should afford the β epimer of 3.

References and Notes

1) M. Naruto, K. Ohno, N. Naruse and H. Takeuchi, Tetrahedron Lett.,251 (1979).

2) G.L. Bundy, ibid., 1957 (1975).

3) A. Guzman and J.M. Muchowski, ibid., 2053 (1975).

4) The 11α-homo-PGE_2 cogener has also been prepared: see references 2, 3 and a) K. Sakai, J. Ide and O. Oda, ibid., 3021 (1975); b) J. Ide and K. Sakai. ibid., 1367 (1976).

5) This work was reported at the 176th ACS Meeting, Miami, Florida, September 1978, Organic Section Paper 90.

6) W. Wendt, W.H. Haegele, E. Simonitsch and H. Schmid, Helv. Chim. Acta, 43, 1440 (1960).

7) D.R. Dalton, V.P. Dutta and D.C. Jones, J. Amer. Chem. Soc., 90, 5498 (1968).

8) Details of the scope and mechanism of this new reaction are presently under investigation.

9) Hydrogenation over Ru in wet EtOAc at 100 atm., or with Rh/Al_2O_3 in EtOAc at 1 atm. gave results similar to those obtained with Rh/C.

10) Lactol 14 was oxidized with partial epimerization: Hplc separated 17 from the enantiomer of 18 (15%).

11) J.M. Bobbitt and K-P. Segebarth, "The Iridoid Glucosides and Similar Substances", Chapter 1 in "Cyclopentanoid Terpene Derivatives", W.I. Taylor and A.R. Battersby, editors (Marcel Dekker, N.Y., 1969).

12) We extracted leaves, twigs etc., obtained by pruning adult plants. Aucuba japonica is a very common plant. Our source: Ingleside Plantation Nurseries, Oak Grove, Westmoreland County, Va.

13) R.B. Duff et al., Biochem. J., 96, 1 (1965).

14) P. Karrer and H. Schmid, Helv. Chim. Acta 29, 525 (1946).

15) A.J. Birch, J. Grimshaw and H.R. Juneja, J. Chem. Soc., 5194 (1961).

16) This compound gave a satisfactory elemental analysis.

17) High Field NMR spectra were obtained at the Southern New England High Field NMR Facility at Yale University (270Mc) or at Rockefeller University (220Mc).

18) Ms. B. DeBarbieri (Hoffmann-LaRoche) was the gracious source of the high resolution mass spectra. Medium resolution (CI) spectra were obtained at Rockefeller University.

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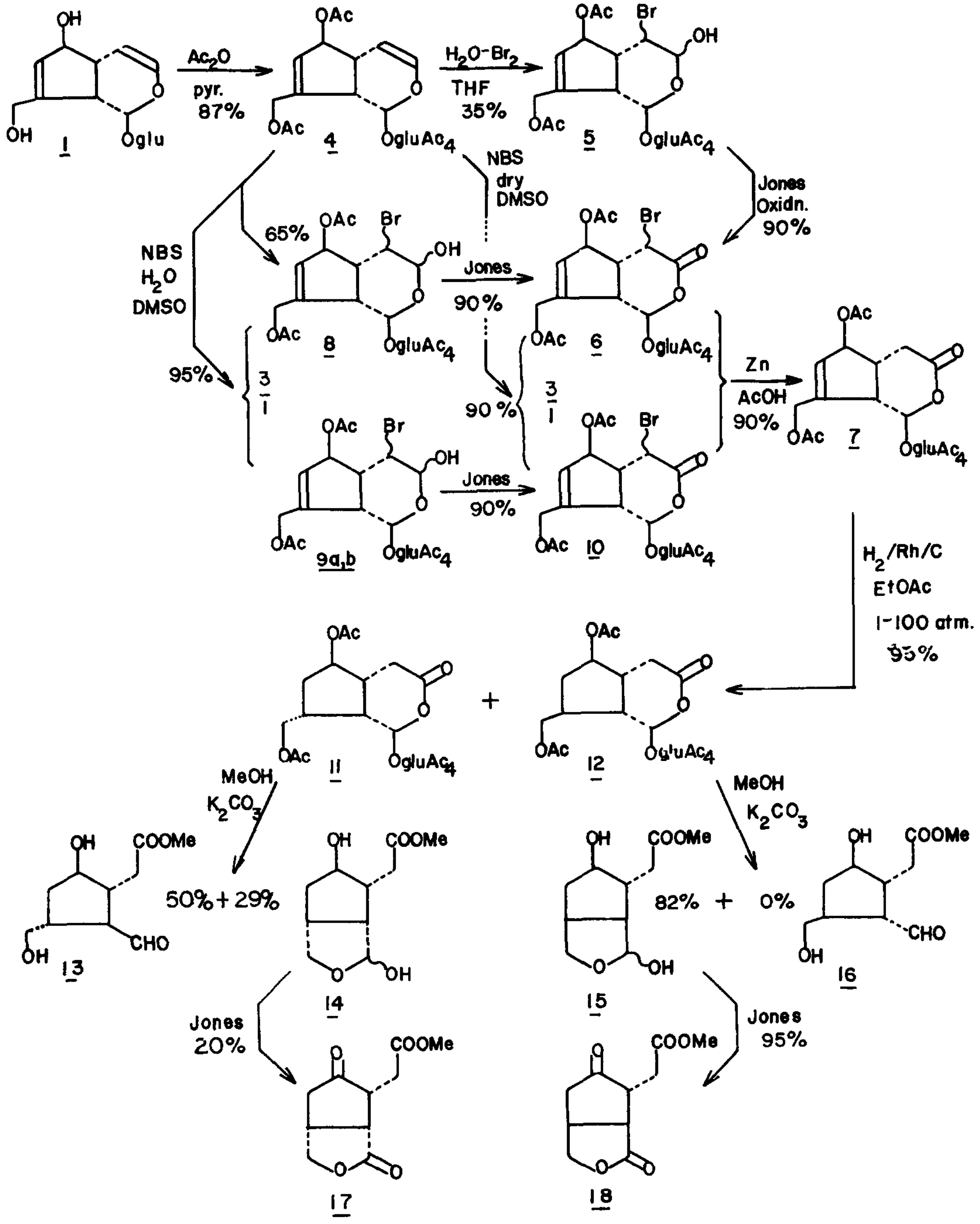
SCHEME I


1
4
5
Ac2O
pyr.
87%
H2O-Br2
THF
35%
NBS
dry
DMSO
Jones
Oxidn.
90%
NBS
H2O
DMSO
95%
3/1
65%
8
Jones
90%
6
90%
3/1
9a,b
Jones
90%
10
Zn
AcOH
90%
7
H2/Rh/C
EtOAc
1-100 atm.
95%
11
12
MeOH
K2CO3
13
50% + 29%
14
MeOH
K2CO3
15
82% + 0%
16
Jones
20%
17
Jones
95%
18
OH
OAc
Br
Oglu
OgluAc4
COOMe
CHO

Compound	Best% Yield	Mp°C	$\alpha_D^{23.1°C}$	Additional Data
1	1.0	179-80	--	Lit.mp. 181[14]
4	87	127-7.5	-160.9	" " 128[15]; Lit. $\alpha_D^{15°C}$ -156.6[15]
5	36	150-1d	--	" " 150d[6]
6[16]	90	165-5.5	-80.0	" " 165-6[6]
7[16]	92	174-4.5	-77.0	" " 174-5[6]
8[16]	65	135-6	--	
10[16]	90	122-3	-90.8	
11[16]	47	140-1	-22.4	
12[16]	80	133-4	-28.8	" " 133-4[6]
13	50.2	oil	+10.5	M/e 217.1067 (calc. for M^++H: 217.1078)[18]
14[16]	28.5	72-3	-5.1	
15[16]	82	110-11	-46.8	M/e 200 (M^++H-OH); ^{13}Cnmr: 1CH_3, 3CH_2, 5CH, 1C=O
17[16]	20	111-2	-12.8	M/e 212; ir 1778, 1752, 1738 cm^{-1}
18[16]	95	79-80	+8.1	M/e 212; ir 1783, 1752, 1738 cm^{-1}

Selected ^{1}Hnmr data (δ/$CDCl_3$)[17]

4	H_1: 5.19, d, $J_{1,9}$=4; H_3: 6.19, dd, $J_{3,4}$=6, $J_{3,5}$=2; H_4: 4.94, dd, $J_{4,3}$=6, $J_{4,5}$=3; H_7: 5.88, dd, $J_{7,6}$=2, $J_{7,10}$=1; $H_{10a,10b}$: 4.76, s(br); $OCOCH_3$: 2.125, 2.119, 2.063, 2.055, 2.035.
7	H_1: 5.66, d, $J_{1,9}$=2.5; H_7: 5.91, dd, $J_{7,6}$=1.5, $J_{7,10}$=1.5; $H_{10a,10b}$: 4.707, 4.779, ABq $J_{a,b}$=15.4; $OCOCH_3$: 2.126, 2.111, 2.065, 2.054, 2.000.
11	H_1: 5.62, s; $OCOCH_3$: 2.10, 2.07, 2.05, 2.03, 2.00.
12	H_1: 5.57, d, $J_{1,9}$=2; $H_{10a,10b}$: 4.12 d(br), $J_{10,8}$=6; $OCOCH_3$: 2.096, 2.070, 2.052, 2.037, 2.026, 2.004.
13	CHO: 9.67, d, J=3.
15	OH: 4.81 (DMSO-d_6), d, J=6 (D_2O labile); OH: 5.76 (DMSO-d_6), d, J=4 (D_2O labile); H_1: 5.09 (DMSO-d_6), d, J=4 ($\rightarrow$ s/D_2O); $COOCH_3$: 3.59, s.

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