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# SYNTHESIS OF BRUCEANTIN PRECURSOR: 15-DEOXYBRUCEOLIDE

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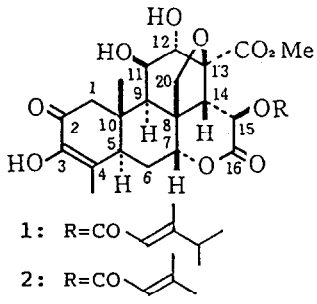
Summary: A 15-deoxybruceolide, 11,12-di-O-acetyl-3-O-t-butyldimethylsilyl ether (3), was synthesized stereoselectively starting from the previously reported ABCE tetracyclic alcohol (5). The authentic sample of 3 was derived from naturally occurring brusatol (2).

Among a large number of quassinoids,[2)] bruceantin (1) and related compounds exhibit remarkable in vivo antileukemic activity.[3)] These quassinoids have many consecutive asymmetric centers and highly oxygenated complex carbon frameworks. Therefore, numerous synthetic approaches to the quassinoids have been reported.[4)] However the antitumor quassinoids have not yet been synthesized. In this paper, we wish to report the first stereoselective total synthesis of a close precursor of bruceantin, 15-deoxybruceolide (3), which has also derived from naturally occurring brusatol (2).[5)]

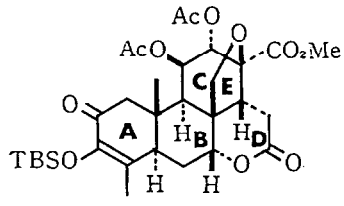


1: R=CO



2: R=CO





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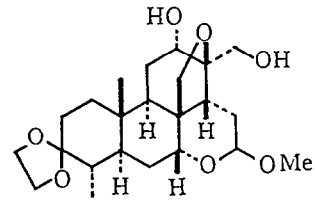


4

We have reported the first synthesis of bruceantin skeleton (4).[6)] Several trial syntheses toward bruceantin (1) utilizing 4 indicated that introduction of a hydroxyl group into C-11[7)] is hard after formation of ring D. Therefore, the present synthesis started from the previously reported ABCE tetracyclic alcohol (5).[6)] Treatment of 5 with potassium hydride and chloromethyl methyl ether in a mixture of THF-DMF (4:1) gave 6 accompanied with the migration of t-butyldimethylsilyl (TBS) group[8)] in 80% yield. Hydroboration of 6 with thexylborane followed by oxidative work-up gave alcohol (7) in 96% yield, whose newly generated hydroxyl group was protected as its methoxymethyl (MM) ether (8, quant.). Allylic oxidation at C-7 position of 8 with Collins' reagent gave α,β-unsaturated ketone 9, which gave corresponding saturated ketone 10 on Birch reduction (37% from 8). The C-7 carbonyl group in 10 was reduced with lithium triethylhydroborate in the presence of lithium bromide in THF to afford desired 7α-alcohol 11 in 89%

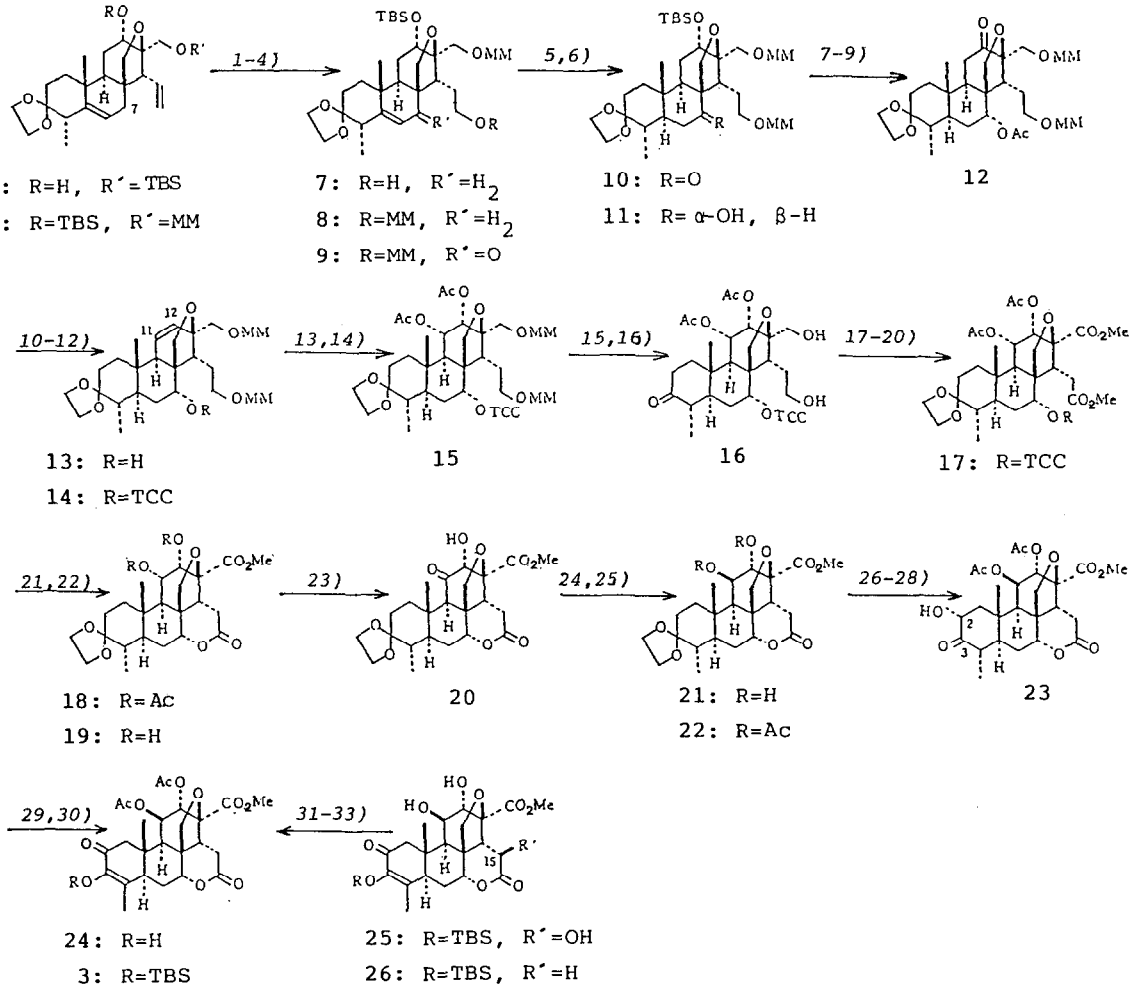
yield along with 10% of its 7β-epimer. The alcohol **11** afforded ketone **12** on successive acetylation (97%), removal of the silyl protecting group (quant.), and Collins' oxidation (99%).

Introduction of a hydroxyl group into C-11 position was considered to be feasible via an olefin precursor having a C-11(12) double bond in view of the literature precedents.[9,10] On treatment with methyl lithium, tosylhydrazone of the ketone **12** afforded olefin **13** in 92% yield.[10] The hydroxyl group at C-7 of **13** was protected with trichloroethoxycarbonyl (TCC) group (2,2,2-trichloroethyl chloroformate, dimethylaminopyridine, pyridine, 98% yield)[11] to give **14**. The choice of a TCC group was dictated by a need to have a protecting group which could be selectively removed in the presence of methoxymethoxyl and acetoxyl groups. Cis dihydroxylation (1. $OsO_4$ in THF-pyridine, 2. $NaHSO_3$, 88% yield) of **14** followed by acetylation (97%) afforded diacetate **15**.

After the introduction of a hydroxyl group into C-11, the next step to be examined was formation of ring D. Selective removal of methoxymethyl groups of **15** was carried out by treatment with ethanedithiol and $BF_3 \cdot Et_2O$[12] being accompanied with acetal exchange giving a thioacetal, whose thioacetal group was removed by treatment with NBS to afford keto diol **16** in 86% yield. The removal of the thioacetal group was necessary for a good yield of the product on oxidation at the next step. The resulting diol **16** was successively subjected to (1) Swern oxidation to give a dialdehyde, (2) Jones' oxidation to give a dicarboxylic acid, (3) treatment with $CH_2N_2$ to give a diester, and (4) acetalization of the carbonyl group at C-3 to afford acetal diester **17** in 82% overall yield. The acetal diester **17** was treated with zinc powder in acetic acid-THF (1:9) and then pyridine[13] to effect selective removal of the TCC group and concomitant lactonization giving rise to pentacyclic lactone **18** in 94% yield.

Elaboration of the trans-diaxial diol (C-11 and C-12) in ring C required inversion of the hydroxyl group at C-11. On this purpose, we employed essentially the same oxidation-reduction method as used by Fuchs[9] and Grieco[10] successfully carrying out following sequence. After removal of the acetyl group of **18** with KOMe in MeOH, the resulting cis diol **19** was treated with 2 equiv of $(COCl)_2$ and 4 equiv of DMSO in $CH_2Cl_2$ at -78 °C for 30 min and then with 8 equiv of $iPr_2NEt$ at -78 °C to room temperature to afford exclusively keto alcohol **20** in 98% yield. Subsequent reduction of **20** with 4 equiv of tetrabutylammonium borohydride in AcOEt at 0 °C gave the desired trans diol **21** in 60% yield.

Formation of the ring A diosphenol moiety of bruceantin (**1**) in **21** was achieved by the following reactions: (1) acetylation of **21** giving **22**, (2) deprotection of the carbonyl group in **22**, (3) trimethylsilyl enol ether formation using TMSOTf and $Et_3N$ and successive MCPBA oxidation of the silyl enol ether giving α-hydroxy ketone (**23**), (4) $Bi_2O_3$ oxidation of **23** to give diosphenol (**24**) in 15% overall yield. The hydroxyl group of the diosphenol




5: R=H, R′=TBS
6: R=TBS, R′=MM

7: R=H, R′=$H_2$
8: R=MM, R′=$H_2$
9: R=MM, R′=O

10: R=O
11: R= α-OH, β-H

12

13: R=H
14: R=TCC

15

16

17: R=TCC

18: R=Ac
19: R=H

20

21: R=H
22: R=Ac

23

24: R=H
3: R=TBS

25: R=TBS, R′=OH
26: R=TBS, R′=H

1)$CH_3OCH_2Cl$,KH/THF-DMF 2)$H-BH_2$/THF($0^oC \rightarrow rt$); NaOH,$H_2O_2$ 3)$CH_3OCH_2Cl$,$(iPr)_2NEt/CH_2Cl_2$ 4)$CrO_3 \cdot 2Pyr/CH_2Cl_2$ 5)Li,$NH_3$,THF 6)$LiEt_3BH$, LiBr/THF ($-78^oC \rightarrow rt$) 7)$Ac_2O$,DMAP/Pyr 8)$Bu_4NF$/THF($50^oC$) 9)$CrO_3 \cdot 2Pyr/CH_2Cl_2$ 10)$TsNHNH_2$,TsOH,$MgSO_4$/THF 11)MeLi/THF 12)$CCl_3CH_2OCOCl$,DMAP/Pyr 13)$OsO_4$/THF-Pyr; aq.$NaHSO_3$ 14)$Ac_2O$,DMAP/$CH_2Cl_2$ 15)$(CH_2SH)_2$, $BF_3 \cdot Et_2O/CH_2Cl_2$($0^oC$) 16)NBS/aq.$CH_3CN$ 17)$(COCl)_2$,DMSO,$Et_3N/CH_2Cl_2$($-78^oC \rightarrow rt$) 18)Jones' oxid. 19)$CH_2N_2$/AcOEt 20)$(CH_2OH)_2$,TsOH/PhH(reflux) 21)Zn/AcOH-THF 22)KOMe/MeOH 23)$(COCl)_2$,DMSO,$(iPr)_2NEt/CH_2Cl_2$($-78^oC \rightarrow rt$) 24)$Bu_4NBH_4$/AcOEt($0^oC$) 25)$Ac_2O$,DMAP/$CH_2Cl_2$ 26)HCl/acetone 27)TMSOTf,$Et_3N/CH_2Cl_2$($0^oC$) 28)MCPBA/$CH_2Cl_2$($0^oC$) 29)$Bi_2O_3$/AcOH(reflux) 30)$tBu(Me)_2SiCl$,imidazole/DMF 31)PhOCSCl,DMAP/Pyr 32)$Bu_3SnH$,cat.AIBN/toluene(reflux) 33)$Ac_2O$,DMAP/$CH_2Cl_2$

24 was protected as its TBS ether to give 3 in a quantitative yield.

The authentic specimen of 3 was derived as follows. Bruceolide TBS ether (25) was obtained from brusatol (2) by known methods.[14] The hydroxyl group at C-15 of 25 was removed to yield 15-deoxybruceolide TBS ether (26) in 65% yield by reduction of phenyl thiocarbonate of 25 with tributyltin hydride and AIBN.[15] On acetylation 26 gave 15-deoxybruceolide 11,12-di-O-acetyl-3-O-t-butyldimethylsilyl ether whose spectroscopic data ($^1$H-NMR, MS, IR, and UV)[16] were completely identical with those of totally synthesized 3.

The final stage of the synthesis toward bruceantin (1), oxidation at C-15 position and esterification, is currently in progress.

## References and Notes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16) Spectral data of 3: IR (KBr) 1745 (broad) and 1680 cm$^{-1}$; UV (EtOH) 271 nm (ε 8300); MS m/z 621 ((M+H)$^+$, 1.6%), 605 ((M-Me)$^+$, 3%), 563 ((M-tBu)$^+$, 100%); $^1$H NMR δ=0.13 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.94 (9H, s, Si-tBu), 1.22 (3H, s, 10-$CH_3$), 1.72 (1H, ddd, J=14.5, 13, and 2.5 Hz, 6β-H), 1.86 (3H, d, J=1.5 Hz, 4-$CH_3$), 2.08 (3H, s, $OCOCH_3$), 2.14 (3H, s, $OCOCH_3$), 2.27 (1H, brd, J=16 Hz, 1α-H), 2.37 (1H, ddd, J=14.5, 2.5, and 2.5 Hz, 6α-H), 2.53 (1H, d, J=16Hz, 1β-H), 2.68 (1H, ddd, J=14, 6, and 1 Hz, 14-H), 2.89 (1H, brd, J=13 Hz, 5-H), 3.10 (1H, dd, J=19 and 6 Hz, 15β-H), 3.26 (1H, dd, J=19 and 14 Hz, 15α-H), 3.70 (1H, dd, J=8 and 1.5 Hz, 20-H), 3.75 (3H, s, $COOCH_3$), 4.72 (1H, t, J=2.5 Hz, 7-H), 4.78 (1H, d, J=8 Hz, 20-H), and 5.11-5.18 (2H, m, 11- and 12-H).


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