Tetrahedron Letters,Vol.30,No.44,pp 5989-5992,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-PICRASIN B[1]

Kenji Kawada, Moonsun Kim, and David S. Watt*

Department of Chemistry, Division of Medicinal Chemistry, and
Lucille Parker Markey Cancer Center, University of Kentucky,
Lexington, KY. 40506

Abstract. An enantioselective total synthesis of (+)-picrasin B (1) from the R-(-)-enantiomer of the Wieland-Miescher ketone (4) employed an A-AB-ABC-ABCD sequence to assemble the tetracyclic skeleton and relied upon a free radical cyclization of an α-bromoacetal to an enone in order to introduce the D ring and a manganese(III) acetate oxidation of a tricyclic enone intermediate in order to introduce the C-11 oxygen substituent.

In developing an enantioselective synthesis of the tetracyclic and pentacyclic quassinoids,[2] we sought an advanced intermediate that would provide access to both subgroups. Although biological activity resided largely in the pentacyclic subgroup,[3] prudence dictated assembly of the tetracyclic group as a suitable vehicle for testing methodology needed for the pentacyclic series. We previously reported[4] a synthesis of a protected tetracyclic diketone 2 in Scheme 1 and our inability to effect oxidation of the C-11 position that was critical to the inversion of the C-9β stereochemistry. Furthermore, the intermediates in the series leading up to 2 lacked the C-4 methyl group of the quassinoid skeleton, and various procedures designed to solve this structural deficiency late in the synthesis failed. We subsequently recast the synthesis in favor of intermediates that incorporated the C-4 methyl group early in the route and intermediates that permitted C-11 oxidation using manganese(III) acetate. The literature contains several ingenious syntheses of tetracyclic quassinoids in racemic form,[5] and we now report an enantioselective total synthesis of (+)-picrasin B (1) from the R-(-)-enantiomer[6] (99% ee) of the Wieland-Miescher ketone (4).

The need for various oxidations and reductions leading up to the tricyclic enone 8 in Scheme 2 demanded the selection of the C-1β methoxy protecting group. The application of Danishefsky's procedure[7] for the preparation of the dienone 5 in combination with the reductive desulfurization of the thiophenoxy-substituted enone 6 led ultimately to the bicyclic dienophile 7 having the correct C-4α methyl group and the AB trans-fused

stereochemistry. The Diels Alder reaction of 7 with 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene[8] provided, following reduction and hydrolysis, the tricyclic diol 8 in excellent yield. Protection of the C-20 alcohol as the benzoate and the C-7α alcohol as the trifluoroacetate ester set the stage for the deprotection of the C-1β methoxy group and acetylation to furnish the C-1β acetate 9.

The rationale for the selection of the protecting groups at C-1, C-7, and C-20 rested principally on the selection of the manganese(III) acetate oxidation procedure[9] that was sensitive to the steric bulk of the C-1 protecting groups and incompatible with free hydroxyl groups at the C-1β or C-7α positions. The manganese(III) oxidation would accomodate either a C-1β methoxy or a C-1β acetoxy group, and in the case of 9, the oxidation secured the C-1β,11β diacetate 10 in which we assumed that the acetate was introduced on the less hindered exo-face of the tricylic system. Our inability to deprotect a C-1β methoxy group in the presence of a C-11β acetate group dictated the order in which the C-1 deprotection and C-11 oxidation operations were assembled. Consequently, as shown in Scheme 3, it was necessary to deprotect the C-1β methoxy group and prepare a C-1β acetate 9 prior to the introduction of the C-11β acetate in 10.

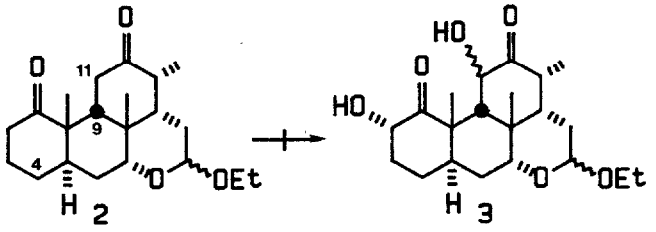
Selective saponification of the C-7α trifluoroacetate in 10 and conversion to the α-bromoacetal 11 permitted the closure of the D ring using the free-radical cyclization[10] to afford the protected δ-lactol 12 as a mixture of C-16 epimers. The stereochemical assignment at C-13 was based on $J_{13,14}$ values of less than 7 Hz for either C-16 epimer, a point that we had not resolved in earlier studies.[4,10,11] Selective saponification of the C-20 benzoate in 12 furnished the C-20 alcohol 13, the pivotal intermediate that we planned to utilize in the synthesis of both the tetracyclic and pentacyclic quassinoid families. The application of this intermediate in the former connection required the reduction of the C-8β hydroxymethyl group to a simple C-8β angular methyl group, a goal that employed the tri-n-butyltin hydride reduction of a C-20 thionocarbonate[12] as the key operation. Further saponification of the C-1β and C-11β acetate groups, Swern oxidation,[11] and methylation provided the O-methyldiosphenol 14 in which the correct C-9α

stereochemistry emerged for the first time. Since we were unable to oxidize the C-2 position directly without competitive oxidation of the C-13 methyl group, we effected the final conversion of 14 to picrasin B (1) through a sequence involving hydrolysis and oxidation of the protected δ-lactol to the δ-lactone, bromination at C-2, acetolysis and hydrolysis. The synthetic material was identical in all respects to the natural product.[13,14]

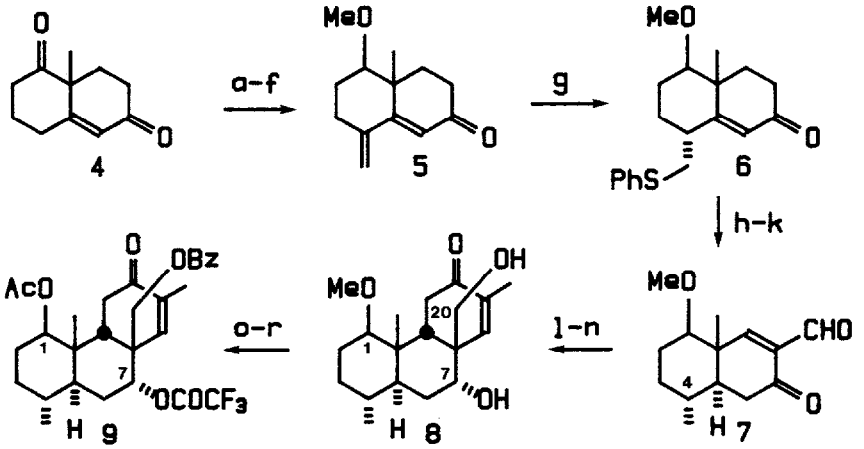
Acknowledgement

We thank the National Institutes of Health (GM 36256) for their generous finacial support and the University of Kentucky for the purchase of bond-issue equipment. We thank the University of Kentucky Mass Spectrometry Center for exact mass determinations.

Scheme 1.

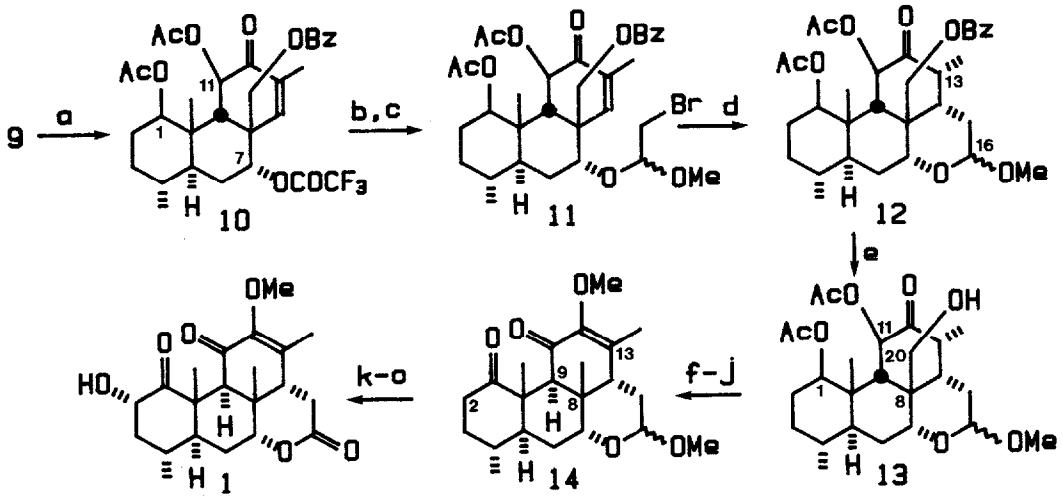



Scheme 2.




a, $NaBH_4$ (95%); b, NaH, MeI (89%); c, TMSCl, $Et_3N$ (94%); d, $[CH_2{=}N(CH_3)_2]I$ (85%); e, $CH_3I$; f, 20% NaOH, EtOAc (85% for e,f); g, PhSH, $K_2CO_3$ (85%); h, Li, $NH_3$; i, PCC (72% for h, i); j, NaH, $HCO_2Et$ (98%); k, PhSeCl followed by $H_2O_2$ (93%); l, $CH_2{=}C(OTMS)C(CH_3){=}CHOMe$ m, Red-Al, n, $H_3O+$ (80% for l,m,n); o, PhCOCl, Py, DMAP (97%); p, TFAA, Py (88%); q, TMSCl, NaI, $CH_3CN$ (92%); r, $Ac_2O$, Py (84%).

Scheme 3.




a, $Mn(OAc)_3$, benzene (89%); b, $(NH_2)_2C=S$, $NaHCO_3$, EtOH (95%); c, $PhNMe_2$, $BrCH_2CH(OMe)Br$ (90%); d, $nBu_3SnH$ (70%); e, $K_2CO_3$, MeOH, 0°C (52%); f, $PhOC(=S)Cl$, Py (78%); g, $nBu_3SnH$ (69%); h, $K_2CO_3$, MeOH, 25°C (51%); i, Swern (63%); j, NaH, MeI (78%); k, 60% aq HOAc; l, $Ag_2CO_3$, Celite (59% for k,l); m, $CuBr_2$, MeOH (44%); n, $Me_4NOAc$ (49%); o, $K_2CO_3$, MeOH, 25°C (50%).

## References


1. This paper is the thirteenth in a series dealing with the synthesis of quassinoids. For the twelfth paper, see Kawada, K.; Kim, M.; Watt, D. S. Tetrahedron Lett. submitted for publication.
2. Kawada, K.; Kim, M.; Watt, D. S. Org. Prep. Proc. Inter. in press.
3. Polonsky, J. Forts. Chem. Org. Naturst. 1973, 30, 101 and 1985, 47, 221.
4. Gross, R. S.; Kawada, K.; Kim, M.; Watt, D. S. Synthet. Commun. in press
5. (a) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. Tetrahedron Lett. 1987, 28, 435; (b) Grieco, P. A.; Ferrino, S.; Vidari, G. J. Am. Chem. Soc. 1980, 102, 7587; (c) Vidari, G.; Ferrino, S.; Grieco, P. A. ibid. 1984, 106, 3539; (d) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. J. Org. Chem. 1982, 47, 602; (e) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. ibid. 1984, 49, 2342; (f) Grieco, P. A.; Parker, D. T.; Nargund, R. P. ibid. 1988, 110, 5568.
6. Hajos, Z. G.; Parrish, D. R. J. Org. Chem. 1974, 39, 1612 and 1615.
7. Danishefsky, S.; Prisby, M.; Lipisko, B. Tetrahedron Lett. 1980, 21, 805.
8. Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N. J. Am. Chem. Soc. 1979, 101, 7001.
9. Dunlap, N. K.; Sabol, M. R.; Watt, D. S. Tetrahedron Lett. 1984, 25, 5839.
10. Kim, M.; Gross, R. S.; Sevestre, H.; Dunlap, N. K.; Watt, D. S. J. Org. Chem. 1988, 53, 93.
11. Kawada, K.; Gross, R. S.; Watt, D. S. Synthet. Commun. in press.
12. Barton, D. H. R.; McCombie, S. W. J. Chem. Soc., Perkin Trans. 1 1975, 1574.
13. For picrasin B (1), $[\alpha]_D$ = +2.1° (c, 6.55 x $10^{-3}$ g/mL, MeOH). For other spectral data, see (a) Viala, B.; Polonsky, J. C. R. Seances Acad. Sci., Ser. C 1970, 271, 410; (b) Hikino, H.; Ohta, T.; Takemoto, T. Chem. Pharm. Bull. (Tokyo) 1970, 18, 219; (c) Hikino, H.; Ohta, T.; Takemoto, T. Phytochemistry 1975, 14, 2473; (d) Polonsky, J.; Tri, M. V.; Varon, Z.; Prange, T.; Pascard, C.; Sevenet, T.; Pusset, J. Tetrahedron 1980, 36, 2983; (e) Park, M. H.; Maeda, M.; Komura, H.; Nakanishi, K.; Nomoto, K. Chem. Pharm. Bull. (Tokyo) 1987, 35, 3082.
14. All intermediates had IR, NMR, exact mass spectral and/or combustion analysis data in accord with assigned structures.


(Received in USA 12 May 1989)