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ON THE STEREOCHEMISTRY OF THE bis-nor-WIELAND-MIESCHER KETONE

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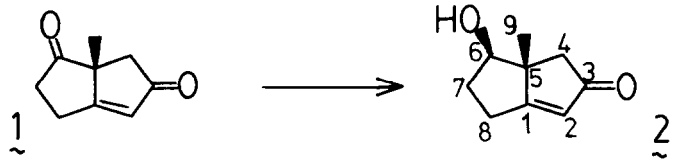
ABSTRACT: The chemo- and stereoselective reduction and the absolute configuration of 5-methylbicyclo[3.3.0]oct-1-en-3,6-dione is reported.

The importance of polycondensed cyclopentanoid natural products led us to suggest that 5-methylbicyclo[3.3.0]oct-1-en-3,6-dione (bis-nor-Wieland-Miescher ketone **1**) might be a versatile building block[1] - a suggestion that has been reinforced by the completion of the total synthesis of coriolin.[2] For its potential to be fully realized, the ability to perform stereocontrolled reactions and the determination of its absolute stereochemistry is vital. The high interest in such natural products induces us to report our recent results on these two areas.

For the determinaton of the absolute configuration, we required one of the alcohols derived from reduction of either carbonyl group. Reduction of the Wieland-Miescher ketone and one of its nor analogues suggested that nucleophilic hydride reducing agents ($NaBH_4$) would exhibit chemoselective reduction of the saturated ketone[3] and more electrophilic ones (B_2H_6) would preferentially reduce the enone carbonyl group.[4] In contrast to these two close analogues, both the "ate" complex from DIBAL-H and n-butyllithium and borane-dimethyl sulfide (THF, -20°) chemo- and stereoselectively reduce the saturated carbonyl group to give **2** (ir 1700, 1630 cm^{-1}) with the latter



reducing agent preferred (78% yield). Eu(fod)$_3$ induced shifts in the 270 MHz ^1H NMR spectrum of **2** suggest that the alcohol and methyl groups are cis to each other. A comparison of the ^{13}C NMR spectra (50 MHz) of **1** and **2** (see Table 1) confirm this conclusion. The assignments are based on chemical shift correlations and single frequency off-resonance decoupling. For the assignment of stereochemistry, the substantial upfield shift of the C(9) methyl carbon due to the increased γ-effect of the cis hydroxyl group and the contrasting

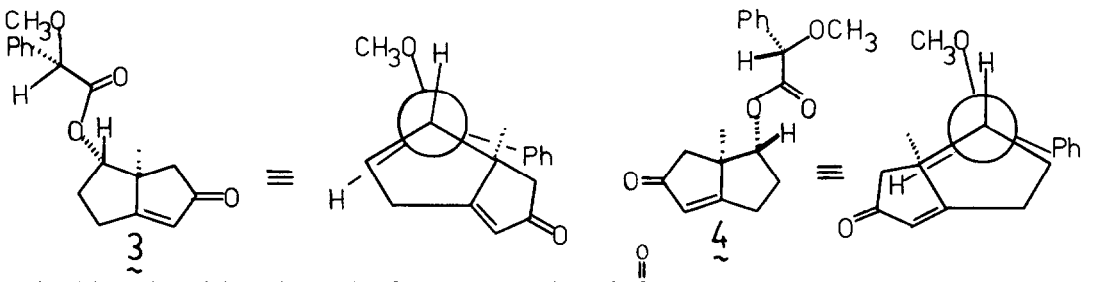
downfield shift of C(4) as a result of its decreased shielding due to relief of the steric compression between the carbonyl oxygen atom and the methylene hydrogens on this carbon closely parallel the shifts seen for reduction of the C(17) ketone in steroids.[5,6]

Table 1. ^{13}C NMR Data

Carbon	1	2	Carbon	1	2
1	184.5	191.2	6	207.1	77.7
2	125.8	125.2	7	38.1	31.9
3	212.1	210.3	8	24.2	24.0
4	44.6	49.7	9	23.0	18.4
5	56.3	53.2			

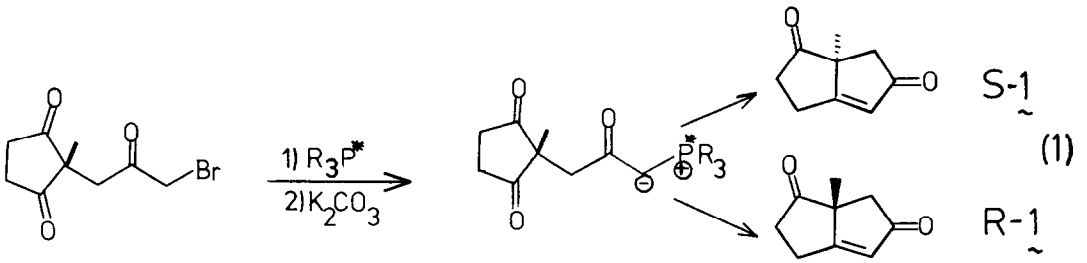
The clean reduction (no detectable amount of a second isomer)[7] from the concave side of the molecule is surprising. None of the normal arguments (ie. steric approach or product development control) appear adequate to rationalize the observations. On the other hand, the orbital distortion model of Burgess and Liotta[8] or the π-bond pyramidalization of Houk[9] appear applicable. Models clearly show that the angular methyl group possesses a perfect geometry for perturbation of the carbonyl π-bond in such a direction to favor approach of a nucleophile from the concave face.

Treatment of the alcohol **2** with (+)-S-O-methylmandelic acid (DCC,DMAP,[10] CH_2Cl_2, rt, 30 min) produced a 1:1 mixture of the diastereomeric mandelate esters **3** and **4**. Using the Mosher model[11] depicted in an "extended Newman"



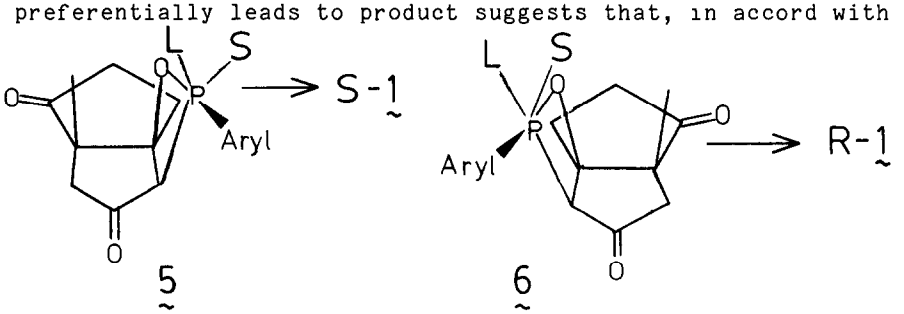
projection in which the circle represents -O-C- in an anti array, we can assign the absolute stereochemistry depicted in **3** to the compound possessing the more upfield methyl group (δ0.74) and methylene group alpha to the carbonyl group (δ 2.05 & 2.47) compared to **4** (δ1.06 and 2.29 & 2.55 respectively). We have found this little used method to be extremely valuable in assigning and analyzing the degree of absolute stereochemistry.[12]

With a good analytical method in hand,[13] we examined a wide range of currently readily available optically active phosphines in order to define the parameters important for asymmetric induction in the intramolecular Wittig reaction utilized to produce **1** (eq. 1).[1] Table 2 summarizes the results. Two types of phosphines were utilized - those which have chirality at phosphorus (Table 2, entries 1-5) and those which have chirality at carbon (Table 2, entries 6-8). In the former case, a trend is clearly visible - two aryl groups or two straight chain alkyl groups lead to low ee. CAMP, which possesses one aryl group and two quite sterically different alkyl groups leads to a



(1)

delightful 87:13 S:R ratio ([α]D +81.0)[16] which increases slightly to 88.5:11.5 at lower temperatures. Since it is generally accepted that, for stabilized ylides, carbonyl addition is reversible and that the elimination from the betaine (and consequently the phosphetane) is the rate and product determining step,[14] a model for this asymmetric induction emerges. The most electronegative group (ie. aryl rather than alkyl) should prefer the apical position. If two different aryl groups are present, either may occupy this position which allows additional diastereomers to become favorable and thus a lower ee. The bigger the difference between L and S, the larger the difference between **5** and **6** and thus the higher the ee as observed. However, the fact that it is **5** and <u>not</u> **6** that preferentially leads to product suggests that, in accord with the



Curtin-Hammond principle, the less stable intermediate is the faster reacting one. On the other hand, such a model does not emerge for the phosphines chiral at carbon. While the steric bulk of the alkyl portion is important (cf entries 7 and 8, Table 2), it is not the only aspect that is important (cf entries 6 and 7).

It appears that **1** can indeed be available in large quantities and with high enantiomeric purity. The ability to recycle the phosphine oxides which are the by-products of the Wittig reaction does impart practicality to the method. For the correct configuration of coriolin (-)-<u>R</u>-**1** and thus (-)-<u>S</u>-CAMP, which is equally readily available,[15] would be needed.

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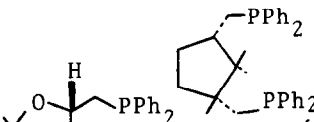
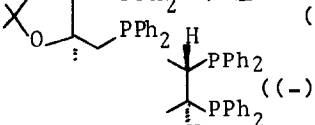
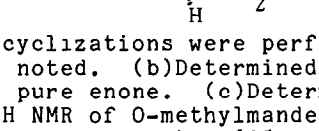
Table 2. Asymmetric Induction[a]

Entry	Phosphine	Chirality of 1	S:R ratio	% ee[h]
1	(+)-S-β-naphthylmethyl phenylphosphine	---	---	0[b]
2	(+)-R-phenyl-O-anisylmethyl phosphine (PAMP)	(+)-S	57.5:42.5	15[b]
3	(-)-R,R-DIPAMP	(+)-S	55:45	10[b]
4	(-)-R-methylpropylphenyl phosphine	(+)-S	65:35	30[c,e]
5	(+)-R-cyclohexyl-O-anisylmethyl phosphine (CAMP)	(+)S	87:13	74[d,e]
		(+)S	88.5:11.5	77[f]
6	 (CAMPHOS)	(+)S	55:45	10[b]
7	 ((+)-DIOP)[f]	(+)S	76:24	52[d,g]
8	 ((-)CHIRAPHOS)	(+)S	62:38	24[b]

(a)Ylide cyclizations were performed at rt in CH_2Cl_2 or $DCCl_3$ except as otherwise noted. (b)Determined by rotation using 113° as an estimate for optically pure enone. (c)Determined by chiral shift reagent. (d)Determined by 270 MHz ^1H NMR of O-methylmandelates **3** and **4**. (e) Corrected for optical purity of phosphine: entry 4 = 69%; entry 5 = 92%. All others based on 100% ee for phosphines. For bidentate phosphines, equimolar quantities of bromoketone and phosphine was employed (f)Corrected for 88% optical purity of phosphines. Wittig reaction run in CH_2Cl_2/PhH at -10°. (g)The configuration of the (+)-DIOP was incorrectly reported in our first paper, ref 1. (h)The chemical yields range from 60-97% and were unoptimized.

References

1. Trost, B.M.; Curran, D.P. J. Am. Chem. Soc. **1980**, 102, 5699.
2. Trost, B.M.; Curran, D.P. submitted for publication.
3. Boyce, C.B.; Whitehurst, J.S. J. Chem. Soc. **1969**, 4547, 2680.
4. Andrews, G.C.; Crawford, T.C. Tetrahedron Lett. **1980**, 693.
5. Breitmaier, E.; Voelter, W. " ^{13} C NMR Spectroscopy," Verlag Chemie, **1974**, p. 204.
6. This data was confirmed by comparison of the acetate derived from **2** with a sample of the trans acetate, prepared by a microbiological route by Dr. Dee Brooks (personal communication, Purdue University). We are very grateful to Dr. Brooks for communicating this unpublished data.
7. Analysis of the crude reaction mixture by 270MHz ^1H NMR showed alcohol **3** to be 95% pure. Further purification was effected by chromatography.
8. Burgess, E.M.; Liotta, C.L. J. Org. Chem. **1981**, 46, 1703.
9. Rondan, N.G.; Paddon-Bow, M.N.; Caramella, P.; Houk, K.N. J. Am. Chem. Soc. **1981**, 103, 2436. Ibid. **1981**, 103, 2439.
10. Alexanian, V.; Hassner,A. Tetrahedron Lett. **1978**, 4475.
11. Dale, J.A.; Mosher, H.S. J. Am. Chem. Soc. **1973**, 95, 512.
12. Trost, B.M.; O'Krongly, D.; Belletire, J.L. J. Am. Chem. Soc. **1980**, 102, 7596. Trost, B.M.; Belletire, J.L; unpublished results. Trost, B.M.; McDougal, P. unpublished results.
13. Analytical TLC analysis showed complete consumption of starting alcohol **2**. The esters were typically isolated in >90%. The chromatographic mobility of **3** and **4** was very similar. Only partial separation was observed after repeated recycling on analytical HPLC.
14. House, H.O. "Modern Synthetic Reactions," W.A. Benjamin, Inc. **1972**, p. 702-708.
15. Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. Adv. Chem. Ser. 132, 274; Nauman, K.; Zon, G.; Mislow, K. J. Am. Chem. Soc. **1969**, 91, 7012.
16. Corrected for 92% optical purity of phosphine.

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