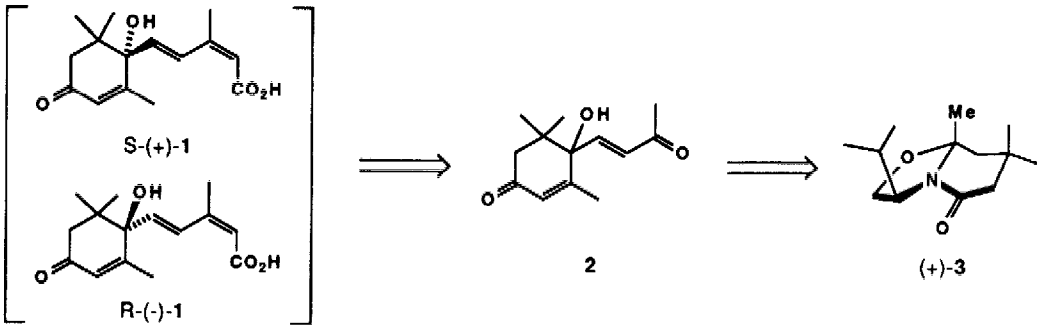
Tetrahedron Letters,Vol.30,No.14,pp 1741-1744,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE ASYMMETRIC TOTAL SYNTHESIS OF (-)-DEHYDROVOMIFOLIOL. THE PENULTIMATE PRECURSOR TO (-)-ABSCISIC ACID (ABA)

A. I. Meyers* and Michael A. Sturgess
Department of Chemistry, Colorado State University, Fort Collins, CO 80523 USA

Summary. A formal total synthesis of (-)-ABA from the chiral bicyclic lactam (**3**) has been accomplished in nine steps.

(+)-Abscisic acid (ABA) **1** has been isolated from numerous plant species and is now well established as an important growth regulator in most plants.[1,2] For many years the absolute configuration of ABA was unknown due to a lack of X-ray crystallographic data and an anomalous CD spectral property. Cornforth[3] originally assigned the absolute

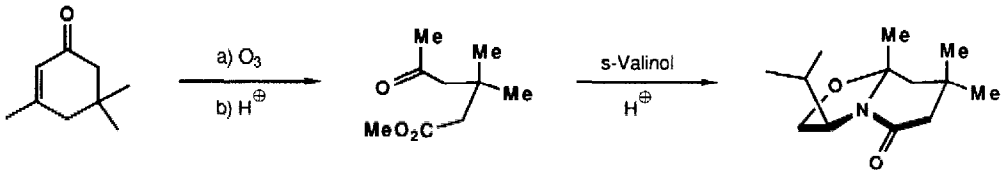


configuration as R (in (-)-**1**), but this was challenged by Burden[4] who reported the conversion of violaxanthin into (+)-ABA ((+)-**1**). Later synthetic studies by Mori,[5] in his enantioselective total synthesis of (+)-ABA, confirmed that the absolute configuration was indeed S. The first total synthesis of (±)-ABA was reported in 1968 by Roberts[6] and involved, as a penultimate precursor, dehydrovomifoliol **2** which was prepared by the allylic oxidation of α-ionone. Wittig olefination of **2** followed by ester hydrolysis gave racemic ABA as a 1:1 mixture of E/Z acids.

Based upon our recently successful asymmetric syntheses of a variety of quaternary substituted compounds emanating from chiral bicyclic lactams,[7] we envisioned an asymmetric route to ABA from **3**. Furthermore, Robert's intermediate, dehydrovomifoliol **2**, seemed to be the logical point of interception in reaching (+)- or (-)-ABA. As an added

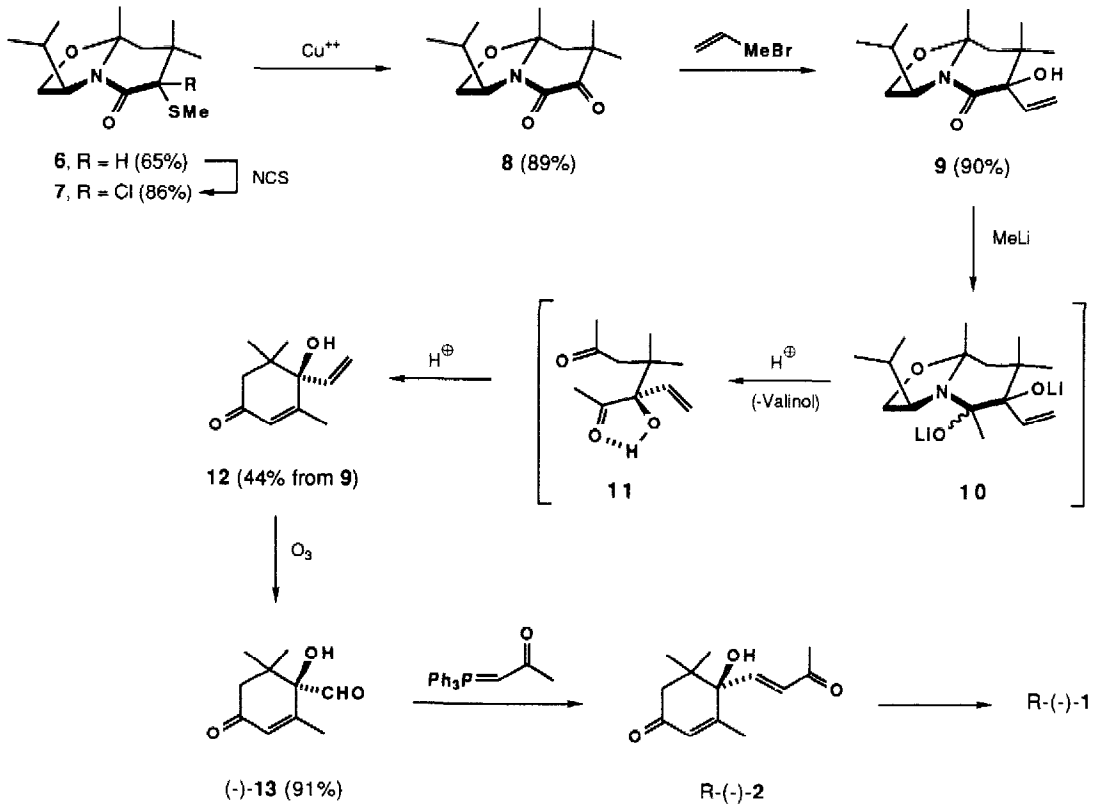
incentive for this study, there was the discrepancy in optical purity of **2**. Mori[4] in his effort to establish the absolute configuration of **1** reported $[\alpha]_D^{20}$ 262° for **2**, while Takasugi,[8] who originally isolated **2**, reported $[\alpha]_D^{20}$ 159°.

Our asymmetric synthetic route was initiated by ozonolysis of isophorone **4** (MeOH, 0°, 5 h) followed by sulfuric acid mediated decarboxylation (reflux, 16 h) to give the keto



4 **5** (+)-**3**

ester **5**. Without purification, the latter was heated with S-valinol and a trace of camphorsulfonic acid in toluene for 96 h to furnish (+)-**3** (oil, bp 114°; 2 mm Hg, $[\alpha]_D^{20}$ 47.5°,



c 1.9, CH_2Cl_2) in 54% overall yield. The α-keto group in **8** was introduced by initial thiomethylation (LDA, $MeSSO_2Me$, -78°, THF) to give the *endo* derivative **6** (65%, mp 55°, $[\alpha]_D^{20}$ 109°, c 1.0, CH_2Cl_2). Attempts to introduce the second thiomethyl group gave poor yields, due presumably to the steric bulk of the adjacent geminal methyl groups.[9] The carbonyl group in **8** was subsequently introduced by halogenation of **6** (86%) using the procedure of Gassman[10] (NCS, CCl_4, 2% camphorsulfonic acid) and the crude chloro derivative **7** was directly hydrolyzed[11] ($CuCl_2 \cdot 2\ H_2O$, 95% acetone, 25°C, 4 h) to the keto lactam (89%, mp 69°, $[\alpha]_D^{20}$ -27.8°, c 1.0; CH_2Cl_2). The overall conversion of **8** from **3** was 54%.

The key stereochemical step involved addition of vinyl magnesium bromide (2.0 eq, 1.5 M in Et_2O) to a THF solution of **8** at -100° C, then at -78° C for 20 min. Work-up (pH 2 quench, ether extraction) gave a 90% yield of **9** with less than 1% of the *exo*-vinyl diastereomer. Chromatography (silica, hexane-ethyl acetate 5:1) gave pure **9** (mp 81° C, $[\alpha]_D^{20}$ 1.27°, c 0.8, CH_2Cl_2) in 89% yield. The high stereoselectivity observed in the vinyl Grignard addition is not surprising in view of the excessive substitution present on the β-face of the bicyclic keto lactam **8**.

Addition of methyl lithium (3.5 eq, Et_2O, 25° C, 24 h) to **9** gave the carbinolamine **10** which was not isolated but directly quenched with orthophosphoric acid (3.5 eq, EtOH, 300 eq, H_2O, reflux, 16 h) to generate the diketone, **11**. Under the hydrolysis conditions, it was found that **11** spontaneously cyclizes to the cyclohexenone **12** (44% from **9**, mp 83° C, $[\alpha]_D$ -149°, c 1.2, CH_2Cl_2). Thus, **9** was transformed in **12** without isolation of intermediates. In view of the two possible modes of aldolization, it was indeed fortunate that **11** cyclized as shown. We believe the hydrogen bonding in **11** enhances the electrophilic nature of the more hindered carbonyl group inhibiting the alternate route to the isomeric cyclohexenone. Ozonolysis to the aldehyde **13** proceeded smoothly (O_3, CH_2Cl_2, pyridine -78°, 20 min, Me_2S) and produced the product in 91% yield (mp 119° C, $[\alpha]_D^{20}$ -508°, c 1.7, CH_2Cl_2). Side chain extension to **2** was performed using acetonylmethylene triphenyl phosphine[12] and proceeded to give R(-)-**2** (75%, oil, $[\alpha]_D^{20}$ -219°, c 0.4, CH_2Cl_2) which was identical except for chiroptical data to Mori[5] and Takasugi,[8] and Roberts.[6] We obtained a negative sign of rotation (219°) which was intermediate between Mori's value (266°) and Takasugi's (159°). A search for a possible racemization step in our scheme for the transformation **9** to **12** proved negative after **12** was subjected to the hydrolysis conditions. Final proof that our material **2** was of high enantiomeric purity came from a chiral lathanide shift study on racemic **2**, prepared *via* Roberts route.[6] Addition of 0.8 eq $Eu(hfc)_3$ to racemic-**2** showed clean separation of the enantiotopic ketonic methyls and comparison with (-)-**2** from this study confirmed its enantiomeric purity as > 95%.

Final Wittig transformation of (-)-**2** to (-)-ABA, **1** was not performed since it is well-known to give a 1:1 E/Z mixture. Use of R-valinol in the formation of (-)-**3** would undoubtedly lead to natural material although the (-)-enantiomer is also known to be biologically active.[2]

Acknowledgment. Financial support for this work was obtained from the National Institutes of Health.

References and Notes

1. Addicot, F. T.; Lyon, J. L.; Ohkuma, K.; Thiessen, W. E.; Carns, H. R.; Smith, O. E.; Cornforth, J. W.; Milborrow, B. V.; Ryback, G.; Wareing, P. F. *Science*, **1968**, *159*, 1493.
2. Walton, D. C. In *Abscisic Acid*; Addicot, F. T., Ed; Praeger Press: New York, 1983, Chapter 4.
3. Cornforth, J. W.; Draher, W.; Milborrow, B. V.; Ryback, G. *Chem. Comm.* **1967**, 114.
4. Burden, R. S.; Taylor, H. F. *Tetrahedron Lett.* **1970**, 4071.
5. Mori, K. *Tetrahedron*, **1974**, *30*, 3566. For another enantioselective synthesis of (+)-ABA, see: Kienzle, F.; Mayer, H.; Minder, R. E.; Thommen, H. *Helv. Chim. Acta.* **1978**, *61*, 2616.
6. Roberts, D. L.; Heckman, R. A.; Hege, B. P.; Bellin, S. A. *J. Org. Chem.* **1968**, *33*, 3566.
7. Meyers, A. I.; Sturgess, M. A. *Tetrahedron Lett.*, **1988**, *29*, 5339. For further examples see Meyers, A. I.; Romine, J.; Fleming, S. A. *J. Am. Chem. Soc.* **1988**, *110*, 7245 and earlier references cited therein.
8. Takasugi, M.; Anetai, M.; Katsui, N.; Masemune, T. *Chem. Lett.* **1973**, 245.
9. In the absence of the geminal methyl groups, *bis*-thiomethylation occurs smoothly. See ref. 7
10. Gassman, P.; Lui Jr., B.-W; Luh, T. Y. *J. Org. Chem.* **1977**, *42*, 1344.
11. Gregoire, B.; Carre, M.-C; Caubere, P. *J. Org. Chem.* **1986**, *51*, 1419.
12. Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41.

(Received in USA 22 December 1988)