Tetrahedron Letters,Vol.28,No.27,pp 3095-3098,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

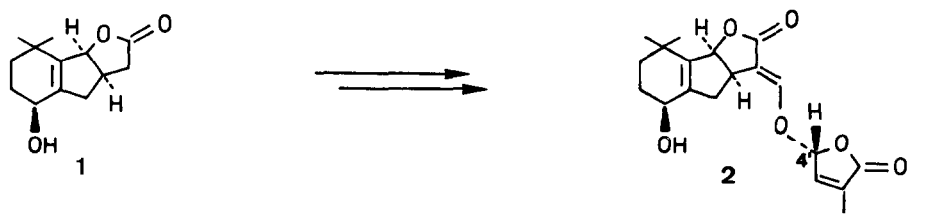
A (FORMAL) TOTAL SYNTHESIS OF (+) - STRIGOL, THE WITCHWEED GERMINATION FACTOR

Ulrich Berlage, Jürgen Schmidt, Zenka Milkova, and Peter Welzel*

Fakultät für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum (FRG)

Abstract - A synthetic route to (+)-1 commencing from (S)-malic acid and 20 is reported. Key steps are the coupling of 20 and 15 to give 21, an intramolecular Wittig reaction (25→27), and an oxidative cyclization (28→1).

(+)-Strigol, which is extremely active in breaking dormancy of Striga seeds, was isolated from root exudates of cotton (Gossypium hirsutum L.) by Cook and co-workers. Constitution and relative configuration were established through an X-ray analysis as depicted in formula 2.[1] A number of total syntheses of (±)-strigol have been reported which all proceed via the racemic tricyclic intermediate 1/ent-1.[2] Sih and co-workers have developed an excellent method for the resolution of 1/ent-1. The (+)-isomer was converted into (+)-strigol and (+)-4'-epistrigol, while the (-)-isomer yielded (-)-strigol and (-)-4'-epistrigol.[4] Since at that time the absolute configuration of 1 and ent-1 could not be correlated with their chiroptical properties, the absolute configuration of (+)-strigol remained unknown. It was only in 1985 that Brooks and co-workers determined (+)-strigol to have the absolute configuration as depicted by 2 through separation of the diastereomeric urethanes obtained from (±)-strigol and (R)-(-)-1-(1-naphthyl)ethyl isocyanate [5] and an X-ray analysis.[6]
In the preceding paper in this issue,[3] we have disclosed a novel route to racemic 1/ent-1 which, in principle, should be applicable to the synthesis of (+)-1 as well. Coupling of the lithiated hydrazone 20 with the (R)-iodide 15 was anticipated to furnish (R)-21 which we hoped to convert into (+)-1 via 23 and 28. We planned to prepare (R)-15 from mesylate 19 by nucleophilic displacement with cyanide to give nitrile 16 and elaboration of the nitrile to the iodomethyl group. For the synthesis of 19 (S)-(-)-malic acid is the obvious starting material. The conversion of 3 to 8



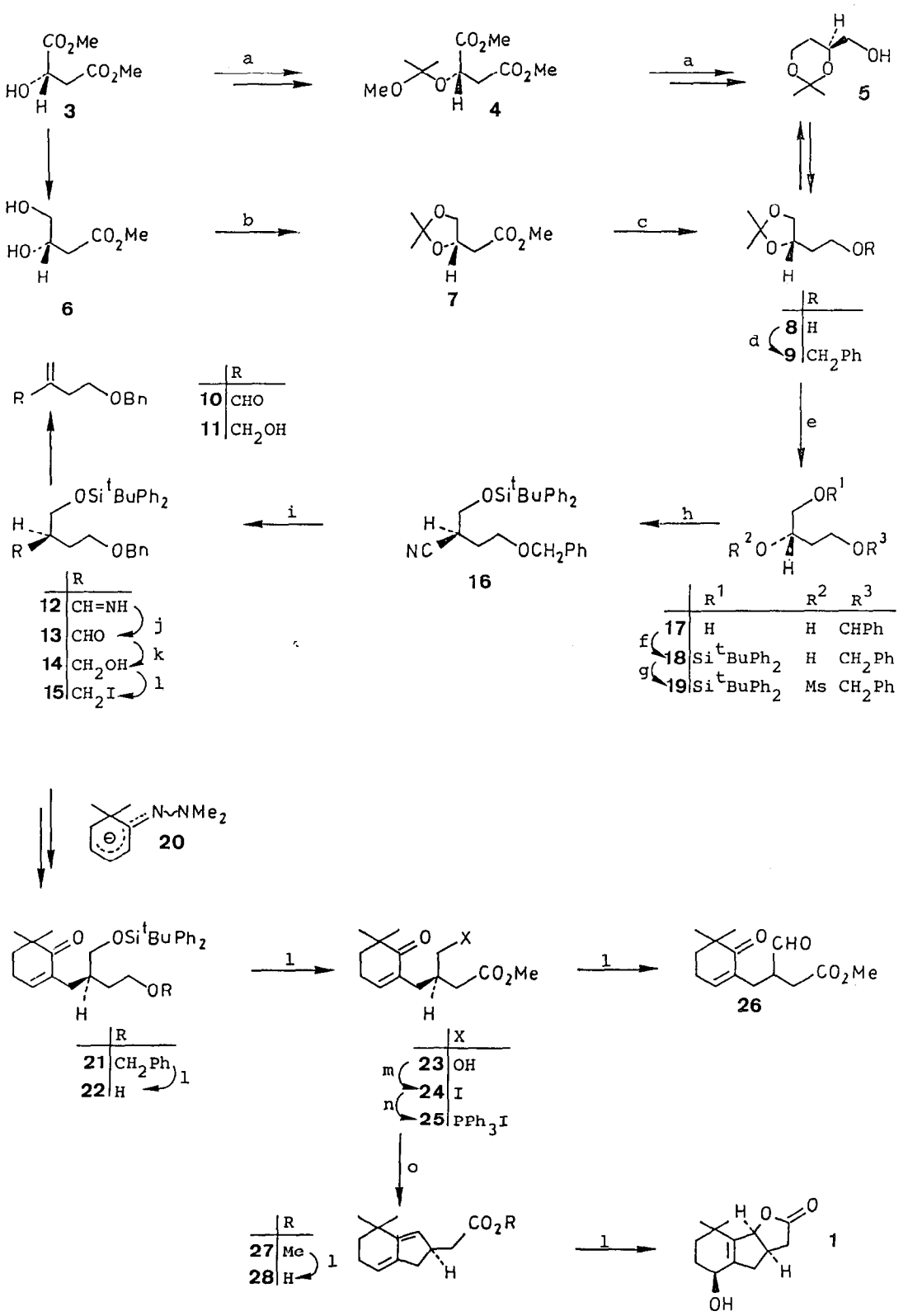
Scheme 1.

was first performed via **4** making use of the Corey procedure [7] which leads to a 9:1 equilibrium mixture of **8** and **5** as shown by Meyers and Lawson.[8] Pure **8** could be obtained by (1) selective reduction of **3** to give **6** as reported by Moriwake and coworkers, [9] (2) acetonide formation, [9] and (3) reduction of **7** with $LiAlH_4$. **19** was prepared from **8** by (1) benzylation, (2) cleavage of the acetal protecting group, (3) protection of the primary OH group to give **18**, and (4) mesylation. The cyanide displacement reaction (**19**→**16** [10]) was troublesome under a number of standard conditions and was best performed with benzyl tri-n-butylammonium cyanide and trimethylsilyl cyanide in acetonitrile solution at 90°C.[11] DIBAH reduction [13] of **16** at -78°C followed by hydrolysis of the intermediate imine **12** and chromatographic separation furnished aldehyde **13** (89%) and a small amount of the unsaturated aldehyde **10**. **13** was reduced with $NaBH_4$ giving **14** [10] (80%) along with **11**. Unfortunately, the conversion of **16** to **14** was unavoidably accompanied with considerable racemization. In different runs samples of **14** were obtained with e.e.'s ranging from 40% to 75% [14] according to Mosher ester analysis.[15] Probably at the aldehyde **13** stage racemization occurs (performing the $NaBH_4$ reduction under differing conditions led to samples of **14** with different e.e.). In keeping with this, **13** is very prone to elimination, and the chromatographic purification of **13**, which is necessary to obtain satisfactory results in the subsequent $NaBH_4$ reduction step, has to be performed very carefully; otherwise extensive elimination (to give **10**) occurs.

In order to test the feasibility of our synthetic plan we continued with a partly racemized sample of **14** which was converted into **23** via **15**, **21**, and **22**, [10] essentially as described in the racemic series. [3] Swern oxidation of **23** furnished aldehyde **26** which seemed to be racemic (no optical rotation). Since the attempt to effect the synthesis of optically active **27** via **26** (as in the racemic series [3]) proved fruitless, we resorted to a Wittig route towards **27**. **23** was easily converted to iodide **24** using the Garegg-Samuelsson method [17] but all attempts to prepare phosphonium salt **25** from **24** under the usual reaction conditions were unrewarding. Finally, the desired substitution could be affected under high-pressure conditions [18] to give **25** in 71% yield. The ylide prepared from **25** with methylsulfinyl anion cyclized [19] admirably to give **27** (59%), which was immediately converted to (+)-**1** [4,10,20] by (1) ester hydrolysis and (2) oxidative cyclization with H_2O_2/cat.diphenyl diselenide. [3] After two recrystallizations [21] (+)-**1** had an e.e. of 87% as determined by Mosher ester analysis. [22]

In conclusion, a route to (+)-**1** and hence (by association of our work with that of Sih [4]) to (+)-strigol (**2**) without recourse to resolution has been developed. It is clear from the above that an efficient synthesis of optically pure **15** is urgently required. Further studies are in progress and will be reported in due course.

Acknowledgements - We are deeply indebted to Prof.F.Klärner and U.Artschwager-Perl for their help and advice in preforming the high-pressure experiments. We also wish to thank Dr.Dietrich and Dr.Müller and their staffs for many NMR and mass spectra. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.


3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
1

Scheme 2: Reagents, conditions, yields.
a) ref.[7]; b) ref.[9]; c) **7** + $LiAlH_4$ (0.5 equiv), 1h reflux: 72%; d) (i) at 0°C: to NaH (1.2 equiv) addn. of **8** in THF, (ii) + $C_6H_5CH_2Br$ (1 equiv), 16h at 20°C, (iii) work-up, distillation (55°C/7x10^{-4}PA): 94%; e) **9** + p-TsOH (2.5 equiv) in H_2O, 1h reflux: 77%; f) **17** + $ClSi^tBuPh_2$ in pyridine, 4h at 0°C: 94%; g) **18** + MsCl (1.05 equiv) + Et_3N (2.9 equiv) in CH_2Cl_2, 4h at -78°C, then ⟶20°C: 92%; **19** + benzyl tri-n-butylammonium cyanide (1.11 equiv) + Me_3SiCN (1.05 equiv) in CH_3CN, 39h at at 90°C: 65%; i) (i) **16** + DIBAH (1.5 M in toluene, 2 equiv), -78°C, (ii) -78°C⟶20°C(4.5h); j) 20% aqueous sodium, potassium tartrate, 5h at 20°C: 89% (from **16**); k) **13** + $NaBH_4$ (0.4 equiv) in ethanol, 30 min at -60°C: 80% + **11** (ca. 10%); l) ref.[3]; m) **23** + Ph_3P (1.1 equiv) + imidazole (2.2 equiv) + I_2 in THF, 1h at 20°C: 89%; **24** + Ph_3P (1.65 equiv) in ether, 48h at 70°C and 7 Kbar: 71%; o) **25** in THF + 0.67 M sodium methylsulfinylmethylide-DMSO (1.3 equiv), 4h at 20°C: 59%.

References and Notes

1) C.E.Cook, L.P.Whichard, M.E.Wall, G.H.Egley, P.Coggon, P.A.Luhan, and A.T.McPhail, J.Am.Chem.Soc. **94**, 6198 (1972).
2) For leading references, see ref.[3]
3) U.Berlage, J.Schmidt, U.Peters, and P.Welzel, Tetrahedron Lett., preceding paper in this issue.
4) J.B.Heather, R.S.D.Mittal, and Ch.J.Sih, J.Am.Chem.Soc. **98**, 3661 (1976).
5) W.H.Pirkle, K.A.Simmons, and C.W.Boeder, J.Org.Chem. **44**, 4891 (1979).
6) D.W.Brooks, H.S.Bevinakatti, and D.R.Powell, J.Org.Chem. **50**, 3779 (1985).
7) E.J.Corey, H.Niwa, and J.Knolle, J.Am.Chem.Soc. **100**, 1942 (1978).
8) A.I.Meyers and J.P.Lawson, Tetrahedron Lett. **23**, 4883 (1982).
9) S.Saito, T.Hasegawa, M.Inaba, R.Nishida, T.Fujii, S.Nomizu, and T.Moriwake, Chem. Lett. **1984**, 1389.
10) $[\alpha]_D$-values: a) **16**: +10.6 (c 1.27, CCl_4); b) **14** (75% e.e., from Mosher ester analysis [15]): -4.04 (c 0.99, CCl_4); c) **22** (42% e.e., from Mosher ester ^{1}H NMR analysis): + 6.58 (c 1.25, $CHCl_3$); d) **1** (ca. 40% e.e.): + 2.9 (c 0.42, $CHCl_3$).
11) This method has been used in Woodward's erythromycin synthesis (personal communication by Prof.D.Hoppe, Kiel), see compound **5** in ref.[12].
12) R.B.Woodward et al., J.Am.Chem.Soc. **103**, 3210 (1981).
13) Review: E.Winterfeld, Synthesis **1975**, 617.
14) see footnote 7 in ref.[12]
15) In the 400 MHz ^{1}H NMR spectra the $CH_2OSi^tBuPh_2$ signals of the two diastereomeric Mosher esters [16] (two sets of 8 lines at δ=3.51-3.66) were sufficiently separated to permit the d.e. to be determined.
16) J.A.Dale, D.L.Dull, and H.S.Mosher, J.Org.Chem. **34**, 2543 (1969).
17) P.J.Garegg and B.Samuelsson, J.Chem.Soc., Chem.Commun. **1979**, 978.
18) Reviews: K.Matsumoto, A.Sera, and T.Uchida, Synthesis **1985**, 1; K.Matsumoto and A.Sera, Ibid. **1985**, 999.
19) H.E.Zimmerman and L.M.Tolbert, J.Am.Chem.Soc. **97**, 5497 (1975). Review: K.B.Becker, Tetrahedron **36**, 1717 (1980).
20) Identical with an authentic sample.[3]
21) First the racemate (**1**/ent-**1**) crystallized.
22) The diastereomeric Mosher esters [16] were analyzed by HPLC (5 µm silica gel SI 100 (Merck), i-octane - tert-butyl methyl ether 1:1, UV detection at 219 nm).

(Received in Germany 23 March 1987)