Tetrahedron Letters, Vol.31, No.47, pp 6823-6826, 1990
Printed in Great Britain

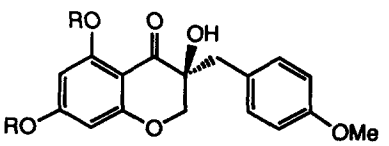
0040-4039/90 $3.00 + .00
Pergamon Press plc

A HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (R)- AND (S)-5,7-O-DIMETHYLEUCOMOL

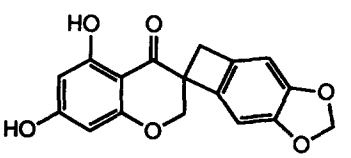
Franklin A. Davis and Bang-Chi Chen*
Department of Chemistry, Drexel University, Philadelphia, PA 19104

Summary: *Both (R)- and (S)-5,7-O-dimethyleucomol* ***1b*** *(R = Me) were synthesized in 57% overall yield in >96% enantiomeric excess. The key step involves the enantioselective α-hydroxylation of the lithium enolate of* ***8*** *by readily available (+)- and (-)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine* ***9c.***

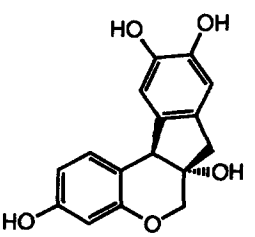
The first member of the homoisoflavanone class of natural products, (-)-(S)-eucomol (**1a**) was isolated by Boehler and Tamm from the bulbs of *Eucomis bicolor* Bak. (Liliaceae) in 1967[1] and its absolute configuration established by X-ray analysis.[2] Since that time other structurally related members of this class have been identified, including the homoisoflavanone types scillascillin **2** and brazilin **3**.[3] A number of related homoisoflavanones have recently been isolated from the roots of *Ophiopogon japonicus,* a widely used Chinese medicinal plant,[4] and from many other sources.[5] (+)-(R)-Eucomol (**1a**) and the dracaenone type **4** have been isolated from the stems of *D. loureiri,* a traditional medicinal plant of Thailand.[6] There is evidence to suggest that homoisoflavanones of type **1** are the biosynthetic precursors of **2-4**.[3,7] No reports of the asymmetric synthesis of any members of this class of natural products have appeared.



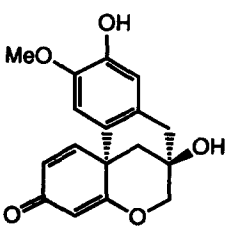
(-)-(S)-**1a**, R = H
b, R = Me



2



3

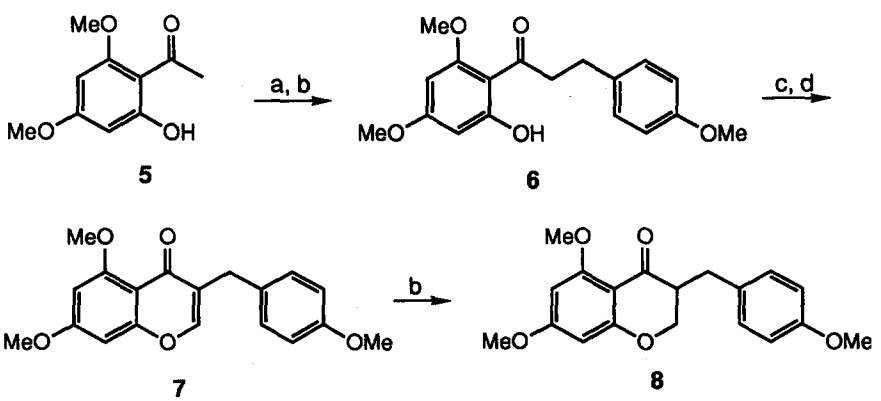


4

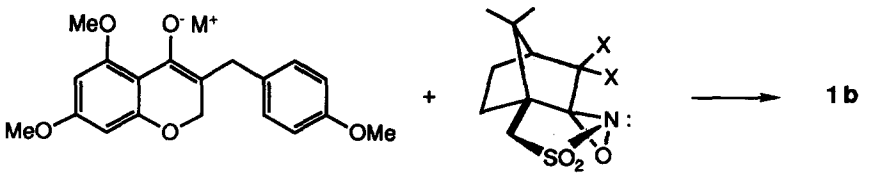
Our interest in the homoisoflavanones and eucomol (**1a**), in particular, is the presence of the tertiary α-hydroxy carbonyl structural unit which is also found in many biologically important natural products.[8] Our recent studies have demonstrated that the most efficient method for introducing a hydroxyl group adjacent to a carbonyl is to oxidize an enolate with an aprotic N-sulfonyloxaziridine oxidizing reagent.[8,9] With an enantiomerically pure N-sulfonyloxaziridine α-hydroxy carbonyl compounds with ee's >95% can often be realized.[8,10] However, the stereoselectivities of these oxidations are unpredictable being dependent on i) the enolate structure ii) the oxidant and iii) the reaction conditions.[10] Our immediate strategy, ultimately aimed at developing more efficient reagents, is to use this protocol in the synthesis of structurally interesting molecules having the α-hydroxy carbonyl moiety. In this context we disclose preliminary results of a highly enantioselective synthesis of both (S)- and (R)-5,7-O-dimethyleucomol (**1b**). (+/-)-Eucomol (**1a**) has previously been prepared in low yield via the hydrogenation of an eucomin epoxide[11] and (+/-)-**1b** by lead tetraacetate oxidation of chromanone **8**.[12]

The multi-step, low overall yield synthesis of 5,7-dimethoxy-3-(4-methoxybenzyl)chroman-4-one (**8**), the enolate precursor of **1b**, has previously been described.[12] Our synthesis of this material is considerably more efficient affording **8** in five steps from **5** in greater than 79 % overall yield (Scheme). Condensation of **5**[13] with 4-methoxybenzaldehyde in boiling methanol using excess 50% aqueous potassium hydroxide for 15 minutes followed by hydrogenation using 10% palladium on activated carbon in ethyl acetate affords a 91% overall yield of 2'-hydroxy-4',6',4-trimethoxydihydrochalcone (**6**). Ring closure with ethyl formate and sodium sand followed by refluxing the crude product in ethanol containing a catalytic amount of sulfuric acid for 2 hours gives the 3-benzylchromone **7** in 90% yield. Refluxing in acidic ethanol is found to be essential for high yields of **8** as the ^{1}H-NMR of the crude product, following the procedure of Farkas and co-workers,[12] shows a mixture of **7**, and the corresponding *cis*- and *trans*-2-hydroxy derivatives of **8** in a ratio of 1:1:1. Chromanone **8** was obtained quantitatively on hydrogenation of **7**.

Scheme



Reagents: a) 4-MeO-C_6H_4CHO, 50% aq. KOH, MeOH, refluxing, 15 min., 91%; b) H_2, 10% Pd/C, 98%; c) HCOOEt, Na sand, 0 °C to r.t., 14h.; d) EtOH, cat. H_2SO_4, reflux 2h.



M^+=Li, Na (+)-**9**

Table: Asymmetric Oxidation of the Enolate of **8** Using (Camphorylsulfonyl)oxaziridines **9.**

entry	**Oxaziridine 9**	**Conditions** Base	**5,7-O-Dimethyleucomol (1b)** % ee[a] (config.)	% Yield[b]	$[\alpha]^{20}_D$ ($CHCl_3$)[c]
1	(+)-**9a**, X=H	NHMDS	6 (R)	77	+ 4.5°
2	(+)-**9b**, X=Cl	NHMDS	88 (R)	66	+62.8°
3		LDA	71 (R)	70	+50.8°
4	(+)-**9c**, X=OMe	NHMDS	77 (R)	75	+54.9°
5		LDA	≥96 (R)	73	+71.4°
6	(-)-**9c**, X=OMe	LDA	≥96 (S)	72	-71.2°

a) Determined using $Eu(hfc)_3$. b) Isolated yields. c) Literature value for (-)-(S)-**1b**; $[\alpha]^{25}_D$ = -71°.[1]

We next explored introduction of the stereocenter at C-3 via the enantioselective oxidation of the enolate of **8** using one of our recently introduced (camphorylsulfonyl)oxaziridine **9** asymmetric oxidizing reagents.[8,10] Treatment of **8** in THF with 1.2 equiv of lithium diisopropylamide (LDA) or sodium bis(trimethylsilyl)amide (NHMDS) at -78 °C gave the enolate which was oxidized by addition of 1.5 equiv of **9** followed by warming to 0 °C.[10] After quenching with sat. $KHCO_3$, **1b** was isolated by prep. TLC (silica gel) eluting with ether-CH_2Cl_2 (1:19) (Table).[14] Both enantiomers of **1b** were readily prepared because the configuration of the oxaziridine three-membered ring controls the product stereochemistry.[9,10] Thus (+)-**9c** and (-)-**9c** afforded (+)-(R)-**1b** and (-)-(S)-**1b**, respectively (entries 5 and 6).

The highest ee's were observed with [(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**9c**)[15] affording **1b** enantiomerically pure; i.e. ≥96% ee (entries 5 and 6). The high stereoselectivities associated with this reagent may be a consequence of metal chelation between the oxaziridine (methoxy groups) and the enolate stabilizing the transition state.[8,10] Consistent with this hypothesis are the higher ee's observed with the better chelating lithium enolate compared to the sodium enolate, >96% vs 77% (entries 4 and 5).

The enantioselective synthesis of **1b** offers the opportunity for the asymmetric synthesis of other homoisoflavanones because racemic type **1** compounds have been transformed into types **3** and **4**.[7,17]

Acknowledgement: It is a pleasure to acknowledge the support of this investigation by National Institute of Health (Institute of General Medical Sciences) through Grant GM 34014.

REFERENCES

1. Bohler, P.; Tamm, Ch. *Tetrahedron Lett.*, **1967**, 3479.
2. Weber, H. P.; Heller, W.; Tamm, Ch. *Helv. Chim. Acta*, **1977**, *60*, 1388.
3. For a review on homoisoflavanones and biogenetically related compounds, see Heller, W.; Tamm, Ch. *Fortsch. Chem. Org. Naturst.*, **1981**, *40*, 105.
4. a) Zhu, Y.; Yan, K.; Tu, G. *Phytochemistry*, **1987**, *26*, 2873; b) Zhu, Y.; Yan, K.; Tu, G. *Acta Pharm. Sin.*, **1987**, *22*, 679; c) Kaneda, N.; Nakanishi, H.; Huraishi, T.; Katori, T. *Yakugaku Zasshi*, **1983**, *103*, 1133.
5. a) Namikoshi, M.; Nakata, H.; Yamada, H.;.Nagai, M.; Saitoh, T. *Chem. Pharm. Bull.*, **1987**, *35*, 2761; b) Namikoshi, M.; Nakata, H.; Nuno, M.; Ozawa, T.; Saitoh, T. *Chem. Pharm. Bull.*, **1987**, *35*, 3568; c) Namikoshi, M.; Saitoh, T. *Chem. Pharm. Bull.*, **1987**, *35*, 3597; d) Barone, G.; Corsaro, M. M.; Lanzetta, R.; Parrilli, M. *Phytochemistry*, **1988**, *27*, 921; e) Adinolfi, M.; Barone, G.; Corsaro, M. M.; Mangoni, L.; Lanzetta, R.; Parrilli, M. *Tetrahedron*, **1988**, *44*, 4981.
6. a) Meksuriyen, D.; Cordell, G. A. *J. Nat. Prod.*, **1987**, *50*, 1118; b) Meksuriyen, D.; Cordell, G. A. *J. Sci. Soc. Thailand*, **1988**, *14*, 3.
7. Blasko, G.; Cordell, G. A. *Heterocycles*, **1988**, *27*, 445.
8. Davis, F. A.; Weismiller, M. C. *J. Org. Chem.*, **1990**, *55*, 3715.
9. For a review on the chemistry of N-sulfonyloxaziridines, see Davis, F. A.; Sheppard, A. C. *Tetrahedron*, **1989**, *45*, 5703.
10. Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.*, **1990**, *112*, 6679.
11. Farkas, L.; Gottsegen, A.; Nogradi, M. *Tetrahedron*, **1970**, *26*, 2787.
12. Krishnamurty, H. G.; Parkash, B.; Seshadri, T. R. *Indian J. Chem.*, **1974**, 554.
13. Dave, K. G.; Telang, S. A.; Venkataraman, K. *J. Sci. Ind. Research*, **1960**, *19b*, 470; *Chem. Abstr.* **1961**, *55*, 16531d.
14. 5,7-O-Dimethyleucomol had properties identical to reported values.[1]
15. Oxaziridines (+)- and (-)-**9c** were prepared by treatment of (-)- or (+)-(3-oxocamphor-sulfonyl)imine[16] with trimethyl orthoformate, a catalytic amount of of H_2SO_4 and Amberlist-15 ion exchange resin in MeOH to give the corresponding sulfonylimines (95%); mp 186-7 °C; $[\alpha]^{20}_D$ = +7.2° (c 3.6 $CHCl_3$) and $[\alpha]^{20}_D$ = -7.3° (c 3.4 $CHCl_3$). The imines were oxidized in the usual manner[8,10] with >95% m-CPBA/sat. K_2CO_3 to give (+)-**9c** (95%); mp 189 (d) °C; $[\alpha]^{20}_D$ = +91.2° (c 3.30 $CHCl_3$) and (-)-**9c** (96%) mp 189 (d) °C; $[\alpha]^{20}_D$ = -91.3° (c 3.39 $CHCl_3$). Details of the synthesis of these oxaziridines will be described elsewhere: Davis, F. A.; Kumar, A.; Chen, B-C.; *J. Org. Chem.* In Press.
16. Glahsl, G.; Herrmann, R. *J. Chem. Soc. Perkin I*, **1988**, 1753.
17. Dann, O.; Hofmann, H. *Chem. Ber.* **1965**, *98*, 1498.

(Received in USA 28 August 1990)