Original citation:

Permanent WRAP URL:
http://wrap.warwick.ac.uk/93619

Copyright and reuse:
The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions. Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRAP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher’s statement:
“This document is the Accepted Manuscript version of a Published Work that appeared in final form in Organic Letters. copyright © American Chemical Society after peer review and technical editing by the publisher.
To access the final edited and published work
http://pubs.acs.org/page/policy/articlesonrequest/index.html.”

A note on versions:
The version presented here may differ from the published version or, version of record, if you wish to cite this item you are advised to consult the publisher’s version. Please see the ‘permanent WRAP URL above for details on accessing the published version and note that access may require a subscription.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk
Synthetic Study Toward Total Synthesis of (±) Germine: Synthesis of (±) 4-Methylene germine


‡: Department of Chemistry, Columbia University, New York, NY 10027
‡: Chemical Probe Synthesis Facility, Department of Biological Sciences, Columbia University, New York, NY 10027

Supporting Information

Germin (1, Fig 1) is the parent structure of a number of alkaloids that are esters or polyesters of its hydroxyl groups. Even though it has been known for quite some time, no synthetic effort to germine has been reported. There was considerable interest in the possible use of these and related substances in controlling blood pressure. Our initial synthetic goal was to construct the germine like structure 2, in which all relative stereocenters are introduced with correct stereochemistry. Note that one extra methylene group on C4 of the A ring was added to the hemiketal structure to make the intermediates more stable and to avoid the known sensitivity of such compounds to bases. We hoped to remove this superfluous methylene group in the later stage of the synthesis while retaining the established relative stereochemical configuration at C4.

Fig 1: Structure of germin (1) and 4-methylene germine (2)

The starting material chosen for the germine synthesis was the readily available tricyclic ketone 3. We planned to use the A/B rings of ketone in 3 as the precursors of the A/B rings in germine (Scheme 1). Therefore, the starting enone had to be reduced, to produce the cis A/B fusion. We hoped to do this by applying Kabalka’s method: the reduction of the tosylhydrazone from 3 with catecholborane. This took place as anticipated, giving the tricyclic olefin 4 in 73% yield. Not only was the cis stereochemistry of the A/B system produced, but the double bond was also placed correctly for the oxygenation of ring A. Oxidation of 4 with peracetic acid in DCM, at -10 °C, gave a 4:1 mixture of the epoxides 5α and 5β. The major component was isolated and analyzed by X-ray, to reveal the α-epoxide 5α. For conversion of 5α to the desired β-allylic alcohol 6, the mixture (5α + 5β) could be eliminated and isomerized/equilibrated with aluminum isopropoxide, [Al(OiPr)3], in boiling m-xylene, providing a 1:4 mixture of the allylic alcohols. The major component was confirmed as the more stable 3β-hydroxy-4-methylene compound 6 by X-ray analysis.

Scheme 1: Conversion of 3 to Tricyclic Compound 9

The small amount of unwanted 5α isomer as well as an isomer of 6, could be recycled with the next batch of the epoxides. Taking into account one recycling, the yield for the required conversion of 4 to 6 was 75-80%. Hydroxylation of 6 with osmium tetroxide (OsO4) in the presence of NMO gave a single triol in 81% yield. It was assumed to be 7, and ready for attempted connection to ring C. At the time these experiments were done, there had not been a report of the trapping of an alcohol group by the cation, or...
radical cation, formed from the oxidation of an anisole ring. More recently, examples of this reaction have appeared in the literature. Several oxidations were carried out on 7; some electrochemical, some with CAN, some on various derivatives of 7, such as the diacetate, the acetone, the benzylidene and the mono- and di-TBS derivatives. In the end, we selected direct oxidation of 7 with 2.1 equivalents of CAN in aq acetonitrile at -20 °C. This gave, in greater than 90% yield, the crude dihydroxydienone 8 which was immediately transformed into its acetonic 9, in 71% overall yield from 6. As noted above, the acetonide system of 9 involves a C4 hydroxymethyl group rather than the required hemiketal hydroxy of 1.

Now three problems had to be faced: (1) reduction of the diene 9 to the enone 10; (2) use the cyclohexenone system to introduce the α hydroxyl group at C7; (3) reduce the cyclohexenone ring C to form a required trans B/C system, the precursor of the five member ring needed for further elaboration (Scheme 2).

Scheme 2: Functionalization of Trycyclic system 15

Reduction of the less substituted double bond could be done by the use of the Wilkinson catalyst under hydrogen in equal amounts of benzene and THF. This gave 10 in 85% yield. Introduction of the 7α-hydroxyl was initially attempted by peracid treatment of the enol acetate of 10, but that was unsatisfactory. We, therefore, followed a Marshall protocol: initial reduction of the enol acetate of 10 in 85% ethanol with sodium borohydride, followed by peroxidation of the resulting mixture of homoallylic alcohols 11 with mCPBA in the presence of NaHCO3 to 12, and finally, Swern oxidation to give the hydroxycetone 13 in 57% overall yield from 10. Oxidation by the peracid was assumed (later confirmed) to take place from the α side, because of interference on the β side by the methyl group, which is axial to the B ring. The next task was to find a way to reduce the enone in 13 to the saturated trans fused ketone. Chemical reduction, such as Li/NH3, would be unsuitable because of the elimination of the oxide bridge by any process that would add electrons to the enone system. Catalytic hydrogenation was obviously required, and we hoped that the desired stereochemistry would be favored by putting a bulky TBS group on the axial 7α-hydroxyl, as shown in 14. In fact, reduction of 14 with 10% Pd on charcoal, in the presence of sodium acetate, gave a saturated ketone that, we assumed, could be represented by 15. The correctness of the various assumptions implied in structure 15 was verified by an X-ray structure determination.

We now faced the problem of converting the cyclohexanone ring of 15 into a cyclopentane system (the C ring), functionalized to allow the construction to proceed by transforming 15 into the cyclopentene aldehyde 20. Conversion of 15 to 20 was started by the formation of the TMS enol ether (LHMDS, followed by TMS-Cl-Et3N), which we expected would be mostly the single isomer 16 because of the preference for a double bond parallel to the ring junction in a trans decalin system. Treatment with cat OsO4 for 2 h at rt, and reduction of the ketol 17 (NaBH4, MeOH-THF) gave a vicinal diol mixture 18 in 90% yield from 15. Cleavage (sodium periodate/aq p-dioxane) of 18 gave the dialdehyde 19 (Scheme 3).

The idea had been to cyclize 19 to the cyclopentene aldehyde 20. There are, of course, two possible ways for the dialdehyde to cyclize. Note that the undesired cyclization would involve attack by base on a methylene in 1,3 relationship to the angular methyl group, and that this would favor the alternative methylene thus leading to the correct aldol. Surprisingly, the cyclization with piperidine acetate salt stopped at the aldol state, rather than giving directly the unsaturated aldehyde. Indeed, dehydration was not simple, presumably reflecting the added strain a double bond would place in the trans hydrindane system: heating at reflux a DCM solution of the mesylate (from MsCl/Et3N on the aldol) left the mesylate mixture unchanged. Only by treatment of the mesylate with DMAP in an acetonitrile-THF mixture at 45-50 °C, for 24 h, 20 was obtained, only in 40-50 % yield (overall from 19). It seemed to be a good point to complete the geometry achieved so far in our synthesis of 20, and an X-ray structure of the derivative 21 was obtained.

Scheme 3: Construction of C ring and Preparation of Diene 22 and Dienophile 23

The further elaboration of 20 toward 2 involved transforming it into an alkoxycarbene, which could take part in a Diels Alder cycloaddition with a suitable dienophile. This was done by Wittig reaction with benzylxoxymethyl triphenylphosphorane, easily prepared by deprotonation of the alkylolation product of triphenylphosphine with chloromethyl benzyl ether, to give a suitable diene 22 in 77 % yield. We would, of course, like to get a preponderance of the E-enol ether from the Wittig reaction, so that the following Diels Alder cycloaddition would lead to the correct hydroxyl stereochemistry, protected as its benzyl ether. The E/Z ratio of enol ethers expected from a Wittig reaction is, however, not clear (nor is it understood). Because such enol ethers are mostly made as intermediates to the aldehydes obtained by hydrolysis, characterization of the enol ether geometry is not usually of concern. In the few cases investigated, both isomers are formed. Separation of the predominately E-enol ether (E/Z = 4:1, in our case 22) was unnecessary, as the Z-isomer would be expected to undergo the planned Diels Alder addition with much more difficulty.

The dienophile 23 was synthesized by a Wadsworth-Emmons condensation between siliconaldehyde 24 and the phosphonate 25, accessible by the coupling of 2-cyano-5-methylpyridine with dimethyl methylphosphonate. The Diels Alder adduct 26 was then obtained, in refluxing toluene with 23, in the presence of the inhibitor, 3-tert-butyl-4-hydroxy-5-methylphenolsulfide, in about 88% yield, apparently as a single substance (Scheme 4). We were confident that the correct stereoisomer had resulted because: (1) the dienophile would approach the more accessible face of the diene, i.e. cis to the starred hydrogen (H*) in 22; (2) there should be exclusive endo addition because exo addition would lead to
very severe interference between the TBSO substituent on the
dienophile and the diene. As a result of such endo addition, the
benzylxoy group in the diene and the acyl pyridine of the dienophile
would end up cis to each other in the adduct.

The adduct 26 is obviously capable of easy elimination of the
benzylxoy group, so that risk must be reduced by making the next
step, the addition of the methyl Grignard reagent at low tempera-
ture to the keto group of 26. This could, of course, give either of
two stereoisomers, or a mixture of the two. After many experi-
ments, it was concluded that the major product from MeMgBr
with 26 had the undesired stereochemistry at the newly formed
tertiary alcohol center. While this was disappointing, it had been
shown by H. Yamamoto that the stereochemistry of Grignard
reactions with cyclic ketones could be reversed by previous comp-
xplexation with the trimethylaluminum salt of 2,6-di-tert-buty1-4-
methylphenol (BHT). It was gratifying that this process (toluene, -
78 °C) gave, in 89% yield, a tertiary methyl carbonyl different
from the one previously obtained, and clearly the desired tertiary
alcohol 27a, in addition to 11% of 27b, the undesired isomer ob-
tained previously.

Scheme 4: Diels Alder Cycloaddition, Grignard Reaction and Con-
struction of E-F ring (Completion of A-B-C-D-E-F)

We were conscious that the osmylation could add hydroxyls ei-
ther from the α side, as desired, or from the β side (Scheme 5).
Some assistance to the α side hydroxylation might come from the
7-hydroxyl in ring B, and, additionally, there was interference to
coming from the β side because of the benzoxyl group emerging
from that side. Anyway, we were ready to try the osmylation: 32a
was first protonated with a slight excess of PPTS in dry pyridine,
followed by stirring for 20 h at rt under argon, with about a 20% ex-
cess of OsO4, to give a high yield of two glycols (correct MW
in a 92:8 (33a:33b) ratio). The major isomer 33a was obtained as
solid, but, unfortunately, could not be crystallized. Our expecta-
tion that 33a was the desired glycol was confirmed by NOE inter-
proton distance calculations, combined with DFT calculations
(QM/NMR). The distance between the hydrogens at C15 and C7
in the DFT-optimized geometry of diastereomer 33a (desired
glycol) was measured as 2.58 Å, as it is in the X-ray of germine
1, while the distance between the same hydrogens in the undesir-
able glycol 33b was measured as 3.68 Å. The interproton distance
between C15 and C7 calculated from the NOE effect in our
synthetic glycol (33a) was 2.58 Å, matching to that for the
desired glycol 33a (the details of the study on the stereochemistry
of the two newly created stereocenters at C14 and C15 are de-
scribed in Supporting Information). Thus, the minor component
33b was determined to be the undesired glycol.

Now only one step remained, removal of the benzyl protecting
group from the C16 hydroxyl. Because of the well-known poison-
ing effect of free amino groups on palladium hydrogenation, the
amino group in 34a was first covered by making its hydrochlor-
ide, by treatment with hydrogen chloride in MeOH (the acetoni-
de was also eliminated by that operation). This was followed by hy-
drogen, pressurized to 700 psi, for 20 h at rt with 10% Pd on char-
coal. The yield of debenzyl was essentially quantitative, giving the
structure 34 (the hydrogen chloride salt of 2, Fig 1).

Before OsO4 oxidation, which was to follow, removal of both
silyl groups, the TMS group (E ring) and the TBS group (B ring),
seemed desirable. But, after many attempts, removal of the ter-
tary TMS group was unsuccessful, presumably because of the high
steric hindrance in this particular case. We had partial success
with cesium fluoride (CsF); a large excess of CsF and 31, in an-
hyd DMF solution, were heated at 95-100 °C for 70 h. At this
point, 57% of 32a in which both the TMS on the C-20 hydroxyl
and the TBS group on the C-7 hydroxyl had been removed, was
yielded along with 32b in which only the TBS group was re-
moved. Compound 32b was converted to 32a, by applying the
same reaction conditions (CsF, 95-100 °C, 70 h).

Scheme 5: Introduction of Diol and Deprotection

We now undertook the reduction of the pyridine ring. Before
that it was necessary to protect the tertiary alcohol of the diol 28
to prevent the participation of the tertiary hydroxyl in reactions
such as cyclization to a tetrahydrofuran ring. A TMS ether was
selected for that role (excess TMS-Cl, followed by treatment with
silica gel that removed the primary TMS), to give the alcohol 29.
Cyclization, followed by treatment with triflic anhydride and 2,6-
di-tet-buty1pyridine in DCM, 1 h at -78 °C, led to the pyrimidinum
salt 30, which was immediately hydrogenated, using platinum
oxide in MeOH in the presence of potassium acetate. We expected
the hydrogenation to take place from the α side to give 31 because
of the hindrance by the C20 axial tertiary TMS ether on the β
side. Survival of the olefinic bond in the ring D was, presumably,
the result of hindrance by the axial benzyl ether group on one
side, and the C7 axial TBS ether group on the other. All of these
anticipations were satisfied by the X-ray structure determination
of 31.
Supporting Information (SI):
Available free of charge on the ACS Publications website.

(1) Experimental procedures and Characterization data, 1H- and 13C-NMR spectra, LCMS data, X-ray data for 5, 6, 15, 21, 31 and 35, and (2) Study on the stereochemistry of the C14-OH and the C15-OH in 33a using QM calculation and NOE effects. NMR-NOE spectra of 33a in MeOH-d₄ and benene-d₆ (PDF).

AUTHOR INFORMATION
Corresponding Author
* gjs8@columbia.edu

Present Addresses
‡ Department of Chemistry, Columbia University, New York, NY 10027. ξ St. Olaf College, Northfield, MN 55057. ϑ Warp Drive Bio, LLC, Cambridge MA 02139. ε Fish & Richardson P.C., Wilmington, DE 19801. ¶ Molec. Art Inc, Saint-Lazare Quebec J7T 2M9, Canada. † Chemical Probe Synthesis Facility, Department of Biological Sciences, Columbia University, New York NY 10027. £ Warwick University, UK. \textrm{â} Regulatory Medical Writing, Janssen Vaccines AG., Rehhagstrasse 79, Bern, Switzerland.

REFERENCES

ACKNOWLEDGMENT This research was supported by NIH grants; (R01 GM05147, R01 HL25635) and NSF (CHE-86-12434). The authors acknowledge our colleagues, Professor Gerard Parkin for the X-ray analyses, Professor James Leighton for helping the high pressure hydrogenation, Professor W. Clark Still for helping distinguishing 33a,b, and Dr. John Decatur for NOE experiments for 33a. Dr. Anil K. Saksena of Schering-Plough Corporation is thanked for a generous supply of germine.

REFERENCES


(3) The equilibrium between hemiketal ⇌ hydroxy ketone reduced the number of asymmetric centers to 15 in (+) germine. Our interest was in the synthesis of the (+) germine derivative rather than the (-) isomer, reducing the relative asymmetric center from 15 to 14.


(7) Epoxidation from the α-face of the olefin in 4 is favored due to a steric hindrance from the angular methyl group at the C10, blocking the β-face (more than a steric hindrance from the C6 methylene group on the α-face of the olefin).

(8) Treatment with either lithium diethylamide in THF or aluminium tri-butoxide in refluxing toluene, undesired α-exo-poxide 5α can be opened to give the undesired α-allylic alcohol (an epimer of 6). Further treatment of the undesired α-allylic alcohol with Al(PrO)₃ (m-xylene, 135 °C), equilibrates to the desired more stable β-allylic alcohol 6 (a 1:4 = α:β). Further heating did not alter the ratio. Thus, a mixture of 5α and 5β was treated directly with Al(PrO)₃ in boiling m-xylene. (a) Dauben, W. G.; Fonken, G. J.; Novec, D. S. J. Am. Chem. Soc. 1956, 78, 2579. (b) Eliel, E. L.; Ro, R. S. J. Am. Chem. Soc. 1957, 79, 5992.


(10) We predicted that OsO₄ oxidation might be favored to proceed from the α-side of the olefin, because the β-face of the olefin is severely hindered by an angular (axial) methyl group and the cis A/B ring junction. This suggestion was supported by the success of the subsequent aromatic ring oxidation, a reaction possible only on the newly formed tertiary hydroxy group is both α and axial on the A ring.


(12) This process was well known in the case of steroid dienones. Djerassi, C.; Gutzwiller, J. J. Am. Chem. Soc. 1966, 88, 4537.


(15) We also made 21 by a different route: sodium borohydride, then benzyl chloride on the aldehyde 20, in which the ring A glycol had been deprotected and transformed into a mono p-methoxybenzyl ether. See SI for the conversion of 20 to 21.


(17) (a) McDougal P.G.; Rico, J. G.; Oh, Y.-J.; Condon, B. J. Org. Chem. 1986, 51, 3388. (b) Aszodi, J.; Bonnet, A.; Teusch, G. Tetradedron, 1990, 5, 1579. We made this compound, originally, by ozonolysis of the bis TBS derivative of cis 1,4-butenediol.


(19) The stereochemistry of 27b was confirmed by X-ray analysis of the derivative 35. See SI for the conversion of 27b to 35.


(22) The OsO₄ reaction using 32b gave a single product, presumably the desired glycol. But the yield was lower than that from 32a; also removal of TMS at the hindered C20 alcohol after osmylation was inefficient.

(23) At this point we realized that we did not have enough material (a few milligrams) to go through the several steps needed to remove the extra methylene group on C-4. One would have to restart the whole synthesis. But I (GS) am now 95 years old………..