Communications to the Editor

[Chem. Pharm. Bull. 30(11)4238—4241(1982)]

STEREOSELECTIVE SYNTHESIS OF (±)-SEMBURIN AND (±)-ISOSEMBURIN USING A COMMON BICYCLIC PRECURSOR

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Using the common bicyclic compound 1-oxabicyclo[3.2.1]octan-2-one (1), two isomeric monoterpenes, semburin (6) and isosemburin (7) isolated from Swertia japonica Makino, have been synthesized stereoselectively in racemic forms.

KEYWORDS —— 2,8-dioxabicyclo[3.3.1]nonane; semburin; isosemburin; stereoselective synthesis; kinetic protonation; α-diketone monothioketal

It has been shown[1] that the reaction of 1-oxabicyclo[3.2.1]octan-2-one (1) with an alkylating agent under kinetic conditions can be efficiently directed to give the exo isomer (3) in terms of structural rigidity and this principle was efficiently extended to the protonation reaction converting the exo isomer (3) into the endo isomer (5) in virtually quantitative yield. We describe herein an application of this principle to the stereoselective synthesis of two isomeric monoterpenes, semburin (6) and isosemburin (7), possessing the novel 2,8-dioxabicyclo[3.3.1]nonane skeleton. These two monoterpenes were recently isolated[2] from the volatile oil of Swertia japonica Makino, a herb widely used as a stomachic and the total structures were confirmed by correlating them to D-mannitol and L-glutamic acid.[3] Syntheses of semburin (6) in racemic forms[4] and both semburin (6) and isosemburin (7) in natural configurations[3] have been accomplished, however, these only allow the production of the former in practice.[5] Our basis for the stereoselective synthesis of both isomeric monoterpenes lies in the stereoslective construction of the chiral center at the crucial position on the rigid bicyclic system and its inversion by stereoselective protonation.

Alkylation of 1-oxabicyclo[3.2.1]octan-2-one (1),[6] prepared from norcamphor,[7] with one equivalent of allyl bromide in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C allowed preferential attack of the enolate (2) from the less hindered face to give the exo-substituted lactone (3: $R=CH_2CH=CH_2$) in 86% yield whose newly produced chiral center was matched with the stereochemistry of the 4-position of semburin (6). The exo-lactone (3: $R=CH_2CH=CH_2$), upon exposure to a saturated aqueous sodium sulfate

solution[8] in the presence of LDA at -78°C in THF, was cleanly converted into the endo-lactone (5:R=$CH_2CH=CH_2$) in quantitative yield via the enolate (4) whose newly generated chiral center now corresponding to the C-4 center of isosemburin (7) (Chart 1).

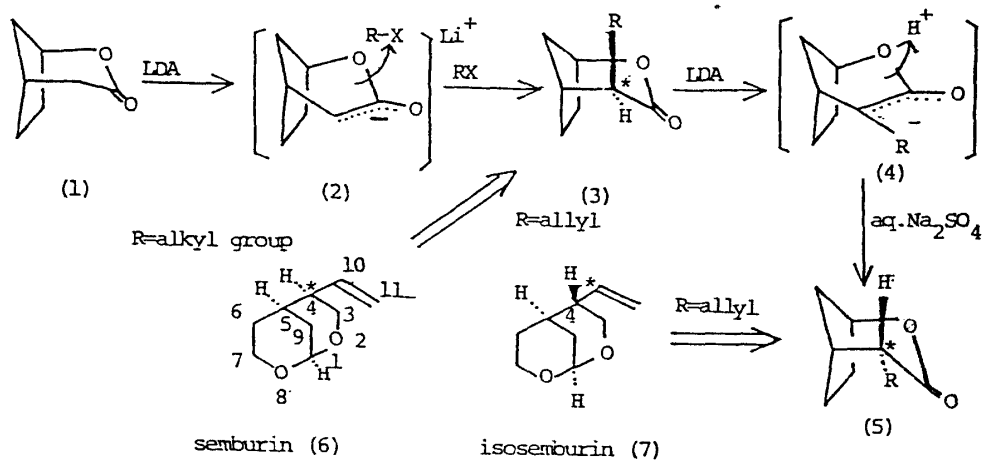
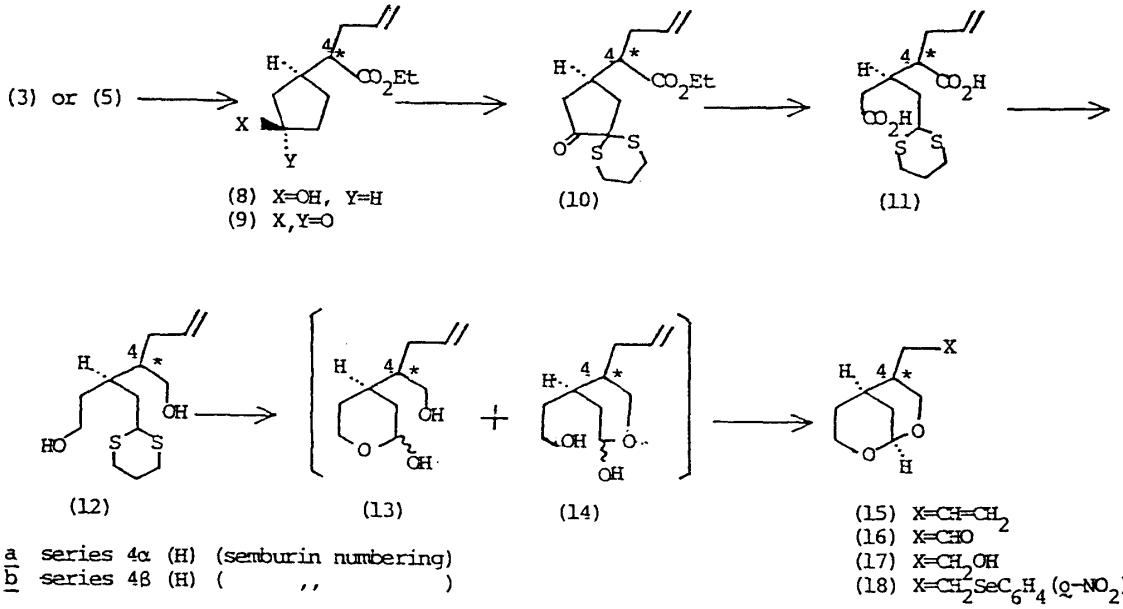


Chart 1

Each lactone was converted into the corresponding monoterpene in a similar manner. Thus, the lactone (3 or 5) was refluxed with excess ethanol[9] to give the monocyclic ester (8)[10] in an excellent yield (≧ 90%). In the reaction conditions partial epimerization occurred to give a minor amount of the inseparable C-4 (semburin numbering) epimer from the each lactone (ca. 30% of the product from the exo-lactone (3) and ca. 10% of the product from the endo-lactone (5)). Without separating the contaminated epimer,[11] each compound (8) was oxidized with Jones's reagent to give the corresponding keto-ester (9) in an excellent yield (≧ 90%). Regioselective introduction of the thioketal group was achieved by treating the pyrrolidine enamine derived from the each keto-ester (9) with trimethylene dithiotosylate in the presence of triethylamine to afford the corresponding α-diketone monothioketal (10)[12] in a moderate yield (∿ 50%). Treatment of each thioketal (10) with potassium hydroxide in tert-butanol at 60°C allowed facile cleavage[12] to give the corresponding diacid (11) in an excellent yield (∿ 90%). Reduction of each diacid (11) with lithium aluminum hydride in refluxing THF gave the corresponding diol (12) in an excellent yield (∿ 90%). On treatment with methyl iodide in aqueous acetonitrile at reflux temperature, each compound underwent smooth hydrolysis of the dithian group[12,13] and concomitant intramolecular hemiacetalization to give a mixture of the alcohols (13) and (14) with corresponding stereochemistry. As in the reported synthesis of (±)-semburine (6),[4] each mixture without purification was refluxed azeotropically in benzene in the presence of pyridinium toluenesulfonate (PPTS)[14] catalyst to furnish the corresponding bicyclic acetal (15) in a good overall yield (∿ 80%). Conversion of the allyl group into the vinyl group was accomplished by employing the established method originally reported by us.[15] Thus, oxidation of each compound (15) with a catalytic amount of osmium tetroxide and two equivalents of sodium periodate[16] in

aqueous THF, followed by reduction of the generated aldehyde (16) with an excess of sodium borohydride in the same flask, afforded the corresponding primary alcohol (17), in an excellent overall yield (∿80%), which was then transformed into the corresponding selenide (18) in a moderate yield (∿50%) by the Grieco's method.[17] The selenide (18a) derived from the exo-lactone (3), on treatment with hydrogen peroxide in aqueous THF,[18] furnished racemic semburin (6) as expected in 66% yield contaminated with 20% of isosemburin (7) which was separated using gas chromatography (SE-30).[18] On the other hand, the selenide (18b) derived from the endo-lactone (5) on the same treatment furnished racemic isosemburin (7) in 70% yield but contamination of the isomer (6) was 13% of the product which was separated using gas chromatography (SE-30).[18]



a series 4α (H) (semburin numbering)
b series 4β (H) (,,)

Chart 2

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have been obtained for the new compounds.
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19) Identical with an authentic material prepared by a different route.[3)]

(Received September 21, 1982)