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ARTICLE TYPE

First Stereoselective Total Synthesis of Neosemburin and Isoneosemburin

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The Claisen rearrangement of sugar derived allyl vinyl ether, Wittig olefination and intramolecular acetalization reactions were used as key steps in the first stereoselective total synthesis of neosemburin and isoneosemburin through the formation of a 3-*C*-branched sugar precursor as a key intermediate.

Introduction

Swertia Japonica Makino (Gentianaceae; Japanese name, semburi) is one of the most important medicinal herbs in Japan even today. The extract of this herb is a widely used galenical remedy for stomach disorders like stomach ache, indigestion, dyspepsia *etc*.[1] The herb tastes extremely bitter and is known to reduce fever, purify blood as well as act as a choleritic.[2] Additionally, semburi was also shown to be pharmacologically active against diabetes[3] and liver disorders.[4] However, certain molecular components of the extract responsible for the medicinal applications have not been fully elucidated. In this context, synthesis and biological study of the individual components of the extract is of great interest. Sakai *et al.* identified 71 steam volatile constituents from the methanolic extract of semburi.[5] Among these, three stereoisomeric mono terpenoids, semburin (**1**), isosemburin (**2**) and neosemburin (**3**) (Figure 1), possessing olefin functionality on a peculiar 2,8-dioxabicyclo[3.3.1]nonane framework have been isolated. A few methods were published on the total synthesis of semburin and isosemburin.[6] However, to the best of our knowledge, the synthesis of neosemburin in either racemic or stereoselective fashion has been not yet reported. In continuation of our efforts towards the synthesis and application of carbon branched sugars, we recently reported an unusual reaction of 3-*C*-branched glycals to produce the 2,8-dioxabicyclo[3.3.1]nonane/nonene motif in a stereoselective fashion.[7] The discovery of this methodology prompted us to investigate its application in the total synthesis of natural products possessing this skeleton. As a consequence, herein, we report our observations towards the first stereoselective total synthesis of neosemburin. Although very few reports have been published recently towards the construction of 2,8-dioxabicyclo[3.3.1]nonane framework,[8] to the best of our knowledge, this is the first report on a successful application of the developed methodology for the total synthesis of a natural product possessing this skeleton.

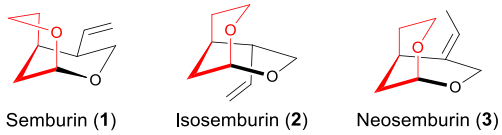

Figure 1 Molecular structure of Semburins.

Results and Discussion

In the initial retrosynthetic strategy, we planned to introduce the *exo*-olefin by Wittig olefination of 2,8-dioxabicyclo[3.3.1]nonane-4-one **4**, which could be obtained by TMSOTf catalysed acetalization of 3-*C*-branched glycal derivative **5**. The synthesis of this 3-*C*-branched sugar derivative could be achieved by the stereoselective Claisen rearrangement of carbohydrate derived allyl vinyl ether **6** (Figure 2, path A).

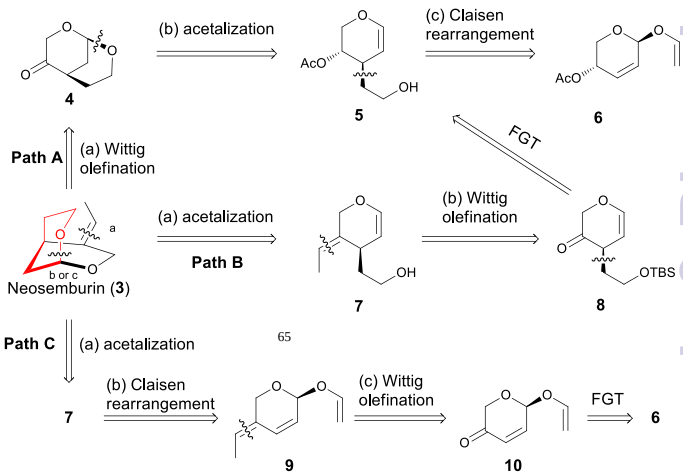

Figure 2 Primary retrosynthetic analysis of neosemburin (**3**). FGT = Functional group transformation.

The desired sugar derived allyl vinyl ether **6** was synthesized from 3,4-di-*O*-acetyl-D-arabinal **11** by following our recent

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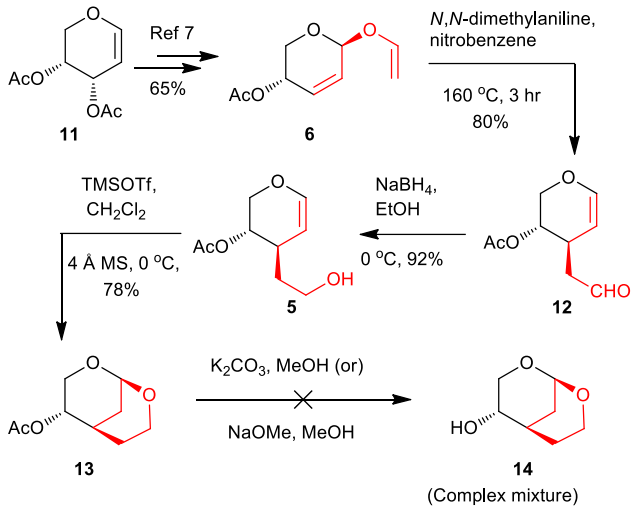
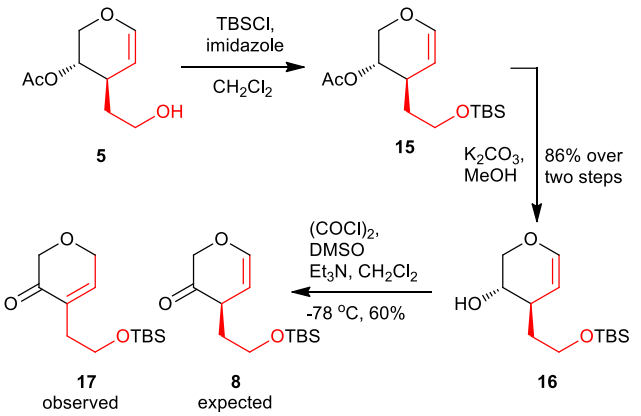
protocol.[7] Compound **6** upon heating in nitrobenzene and *N*,*N*-dimethylaniline at 160 °C for 3 h underwent Claisen rearrangement smoothly and provided the 3-*C*-branched xylal derivative **12** in 80% yield as a single diastereomer.[7] Reduction of aldehyde **12** to alcohol **5** followed by TMSOTf catalyzed acetalization afforded the 2,8-dioxabicyclo[3.3.1]nonane derivative **13** in good yield. The required precursor **4,** for Wittig olefination, would be synthesized by deacetylation of **13** to give alcohol **14** followed by oxidation. Unexpectedly, deacetylation of **13** using catalytic K_2CO_3 or NaOMe in methanol was not successful and provided an inseparable complex mixture (Scheme 1).



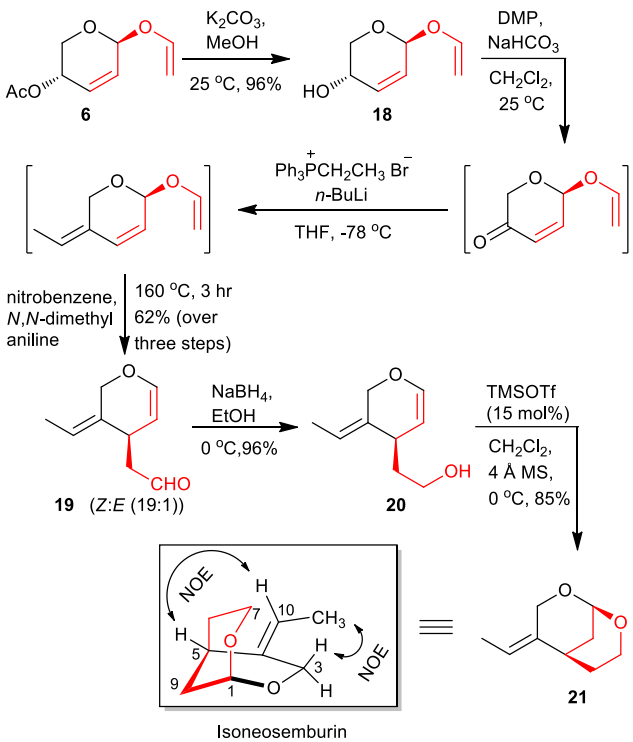
Scheme 1 Synthesis of 2,8-dioxabicyclo[3.3.1]nonane framework present in semburins.

In a revision to our approach, we thought of introducing the exocyclic olefin functionality prior to the formation of bicyclic skeleton (Figure 2, Path B). Therefore, alcohol **5** was protected with TBS to give glycal **15** followed by ester hydrolysis provided hydroxy glycal **16**. However, Swern oxidation of alcohol **16** furnished an undesired product most probably the α,β-unsaturated ketone **17** rather than the expected 3-*C*-branched glycal derivative **8**[9] (Scheme 2).



Scheme 2 Attempted synthesis of neosemburin.

Keeping the above observations in mind, we decided to perform the Claisen rearrangement after incorporation of the *exo*-olefin functionality at C4 position. As shown in Figure 2 (Path C), alcohol **7** could also be synthesized by the Claisen rearrangement of allyl vinyl ether **9** which could be obtained by olefination of ketone **10**. To implement this protocol, compound **6** was deacetylated to give alcohol **18**. Oxidation of **18** with Dess-Martin periodinane (DMP)[10] gave the corresponding ketone and Wittig olefination[11] followed by Claisen rearrangement[12] provided the unstable aldehyde **19** as a single enantiomer possessing a mixture of *Z* and *E* configurations at the olefin in 19:1 ratio,[13] respectively.[14] Immediate reduction of the aldehyde **19** to alcohol **20** followed by acetalization using TMSOTf provided compound **21** in an overall yield of 32% from the commercially available 3,4-di-*O*-acetyl-D-arabinal **11**. The stereochemistry and the double bond geometry in **21** were assigned by observing NOE between 3-H and 10-CH_3, 5-H and 10-H. As the compound **21** possesses an inverted olefinic configuration, with respect to the neosemburin **3** olefinic geometry, it is named as isoneosemburin which is a geometrical isomer of neosemburin (Scheme 3).



Scheme 3 Stereoselective total synthesis of isoneosemburin.

The possible reason for the formation of the *Z*-olefin as a major product might be due to the α,β-unsaturated nature of the precursor ketone that is obtained by the DMP oxidation of alcohol **18**. To obtain the required olefin geometry that is present in neosemburin **3**, a slightly modified protocol was chosen in which the olefination would be performed on an appropriately protected cyclohexanone derivative **23** to obtain the required alcohol **22** (Figure 3).

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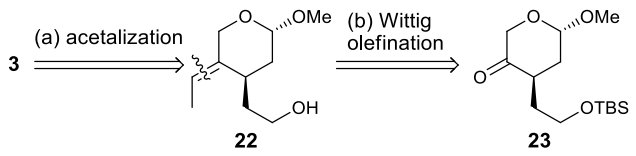
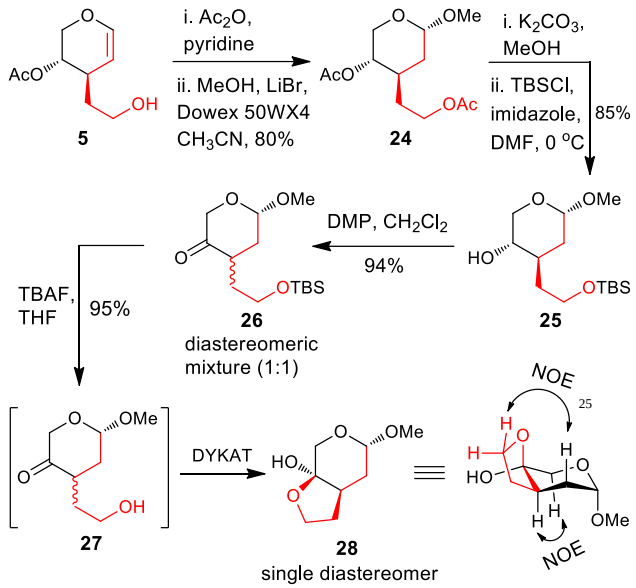


Figure 3 Revised path B retrosynthetic approach towards the total synthesis of neosemburin.

Thus, acetylation of the primary hydroxyl group in **5** followed by acetalization with methanol, LiBr and Dowex 50WX4 in CH_3CN provided the acetal **24** in 80% yield after two steps. Deacetylation of **24** and selective primary hydroxyl protection with TBSCl provided the alcohol **25**. DMP-mediated/Swern oxidation of this secondary alcohol provided ketone **26**. However, the NMR spectra of this ketone revealed that the stereocentre α to the carbonyl was completely epimerized and the compound **26** was found to be a diastereomeric mixture in 1:1 ratio.[15] Surprisingly, deprotection of TBS group using TBAF in THF gave the bicyclic-hemiketal **28** as a single diastereomer *via* the formation of γ-hydroxy ketone **27** (Scheme 4).



Scheme 4 Preparation of a key intermediate for the stereoselective synthesis of neosemburin.

The formation of hemiketal **28** as a single diastereomer from the diastereomeric mixture **26** could be explained by an interesting Dynamic Kinetic Asymmetric Transformation (DYKAT).[16] As shown in figure 4, the two diastereomeric γ-hydroxy ketones, **27a** and **27b**, formed by the TBS deprotection of **26** using TBAF would exist in equilibrium through the formation of an enol intermediate. In the case of diastereomer **27a,** where the 3-*C*-branch is in an axial position, formation of the bicyclic hemiketal **29** might suffer from an increased 1,3-diaxial interaction with the anomeric methoxy group. As a result, the formation of **29** would be a very slow process. On the other hand, diastereomer **27b**, in which the 3-*C*-branch is in an equatorial position, would undergo the intramolecular hemiketalization to give the stable bicyclic hemiketal **28**. Hence, the epimerization as well as the reversible nature of the ketalization might favor the formation of **28** as a single diastereomer. The stereochemistry of **28** has been confirmed by two-dimentional COSY and NOESY experiments.

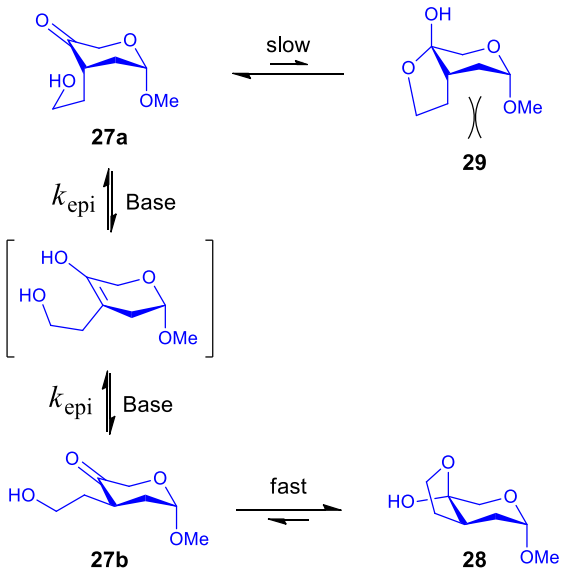
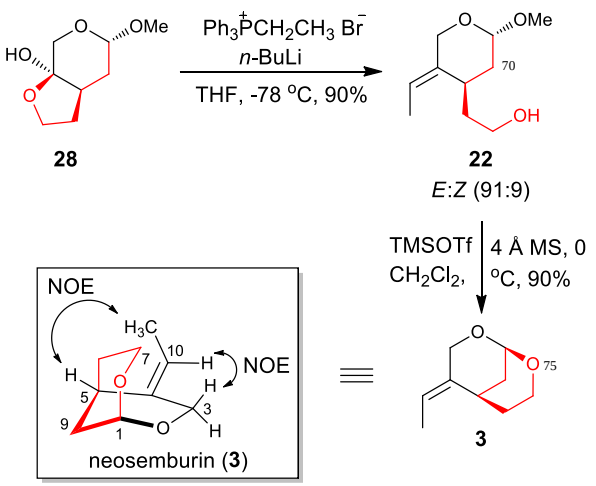


Figure 4 The Dynamic Kinetic Asymmetric Transformation (DYKAT) pathway for the formation of hemiketal **28** as a single diastereomer.

The Wittig olefination of **28** provided the alkenol **22** as a mixture of *E* and *Z* geometrical isomers in 91:9 ratio, respectively. TMSOTf mediated acetalization of **22** afforded the expected natural product, neosemburin **3**[17] in an overall yield of 24% from compound **11** (Scheme 5). The stereochemistry of the double bond is confirmed by observing the NOE between H-5 and 10-CH_3, H-3 and H-10. Further, the NMR data and the optical rotation of the synthetic and isolated neosemburin have complete agreement.[15,18]



Scheme 5 Stereoselective total synthesis of neosemburin.

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Conclusions

In conclusion, the first stereoselective total synthesis of neosemburin has been achieved. In addition, synthesis of isoneosemburin, an unnatural analog of semburin, is also reported. Further, a propitious dynamic kinetic resolution of 4-oxo-3-(hydroxyethyl) sugar derivative is revealed.

Experimental Section

General Methods

All the reactions were carried out under inert atmosphere and monitored by thin layer chromatography (TLC) using silica-gel GF_{254} plates with detection by charring with 5% (v/v) H_2SO_4 in methanol or by phosphomolybdic acid (PMA) stain or by ultra violet (UV) detection unless otherwise mentioned. Benzene, *N*,*N*-diisopropylamine, CH_2Cl_2, THF, MeOH and TMSOTf used in the reactions were distilled over dehydrating agents prior to use. All the chemicals were purchased from SRL, Spectorchem, Merck and Sigma-Aldrich Chemical Companies. Silica-gel (100-200 mesh) was used for column chromatography. ^{1}H, ^{13}C, DEPT, COSY, NOESY spectra were recorded on Bruker 400 MHz or 500 MHz spectrometer in $CDCl_3$. ^{1}H NMR chemical shifts were reported in ppm (δ) with TMS as internal standard (δ 0.00) and ^{13}C NMR were reported in chemical shifts with solvent reference ($CDCl_3$, δ 77.00). IR spectra were recorded on JASCO FT/IR-5300. High resolution mass spectra were recorded on Bruker maXis ESI-TOF spectrometer. Optical rotation was recorded on Rudolph autopol IV polarimeter.

(3S,4R)-4-(2-(tert-Butyldimethylsilyloxy)ethyl)-3,4-dihydro-2H-pyran-3-ol (**16**). To a solution of compound **5** (1.1 g, 5.9 mmol) in CH_2Cl_2 (10 mL) under inert atmosphere was added imidazole (0.8 g, 11.8 mmol) and TBSCl (1.3 g, 8.8 mmol) at 0 °C. The reaction was allowed to reach 25 °C and the reaction mixture was stirred until completion (6 h). The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained crude TBS protected derivative was used in the next step without further purification. A portion of the crude product was subjected to column chromatography to obtain pure compound **15**. R_f = 0.7 (EtOAc/Hexanes, 10%);^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.41 (dd, *J* = 1.7, 6.2 Hz, 1H), 4.90-4.89 (m, 1H), 4.75-4.72 (m, 1H), 3.98-3.90 (m, 2H), 3.75-3.70 (m, 2H), 2.33-2.29 (m, 1H), 2.10 (s, 3H), 1.73-1.66 (m, 1H), 1.55-1.48 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 143.0, 102.2, 70.1, 63.9, 60.0, 38.0, 32.3, 25.8, 21.2, 18.2, -5.4; IR (neat): ν_{max} = 2958, 2860, 1747, 1643, 1468 cm^{-1}; $[\alpha]_D^{25}$: -89.2 (C 1.0, $CHCl_3$); HRMS (ESI): Calcd for $C_{15}H_{28}O_4SiNa$ $[M + Na]^+$ 323.1655, found 323.1656. To the crude product **15** in anhydrous MeOH (10 mL) was added K_2CO_3 (81 mg, 0.59 mmol) and the reaction mixture was stirred at 25 °C until completion of the reaction (3 h). MeOH was completely evaporated under reduced pressure and the crude obtained was purified over silica-gel using hexanes and ethyl acetate to obtain deacetylated derivative **16** (1.31 g, 86%) as a colourless oil. R_f = 0.40 (EtOAc/Hexanes, 10%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.44 (dd, *J* = 2.8, 6.0 Hz, 1H), 4.08 (q, *J* = 8.4 Hz, 1H), 3.88-3.83 (m, 1H), 3.75-3.69 (m, 1H), 3.64-3.58 (m, 2H), 2.21-2.16 (m, 1H), 1.68-1.50 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 103.3, 68.5, 68.1, 62.4, 40.1, 39.0, 25.7, 18.2, -5.4, -5.5; HRMS (ESI): Calcd for $C_{13}H_{26}O_3SiNa$ $[M + Na]^+$ 281.1549, found 281.1550.

4-(2-(tert-Butyldimethylsilyloxy)ethyl)-2H-pyran-3(6H)-one (**17**). To a stirred solution of oxalyl chloride (0.05 g, 0.42 mmol) in CH_2Cl_2 (5 mL), DMSO (0.06 g, 0.84 mmol) was slowly added at -78 °C over a period of 5 min under inert atmosphere and the mixture was stirred for further 15 min at the same temperature. To this, a solution of compound **16** (0.10 g, 0.386 mmol) in CH_2Cl_2 (2 mL) was added slowly over a period of 10 min at -78 °C. Stirring was continued for further 30 min, anhydrous Et_3N (0.192 g, 1.91 mmol) was added slowly at -78 °C and the mixture was allowed to reach 25 °C over 1.5 h. The obtained solution was transferred into a separating funnel and washed with water. The aqueous layer was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude was purified over silica-gel using hexanes and ethyl acetate to obtain compound **17** (0.06 g, 60%) as a colourless oil. R_f = 0.50 (EtOAc/Hexanes, 10%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (t, *J* = 3.2 Hz, 1H), 4.12 (s, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.44 (q, *J* = 7.2 Hz, 1H), 2.43-2.40 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 1H), 0.84 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 144.4, 134.5, 72.1, 65.1, 61.0, 31.8, 25.8, 18.1, -5.4.

(3S,6S)-6-(Vinyloxy)-3,6-dihydro-2H-pyran-3-ol (**18**). To a solution of compound **6** (0.64 g, 3.44 mmol) in anhydrous MeOH (20 mL) was added K_2CO_3 (47.6 mg, 0.32 mmol) and the reaction mixture was stirred at 25 °C until completion (3 h). MeOH was completely evaporated under reduced pressure and the crude was purified over silica-gel using hexanes and ethyl acetate to obtain pure compound **18** (0.48 g, 96 %) as a white solid. R_f = 0.30 (EtOAc/Hexanes, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (dd, *J* = 6.4, 14.0 Hz, 1H), 6.19 (dd, *J* = 5.2, 10.0 Hz, 1H), 5.91 (dd, *J* = 2.8, 10.0 Hz, 1H), 5.25 (d, *J* = 2.8 Hz, 1H), 4.54 (dd, *J* = 1.6, 14.0 Hz, 1H), 4.19 (dd, *J* = 1.6, 6.4 Hz, 1H), 4.08 (dd, *J* = 2.4, 12.4 Hz, 1H), 3.85-3.80 (m, 2H), 2.28-2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 129.9, 126.9, 92.3, 91.8, 64.7, 61.0; IR (neat): ν_{max} = 3216, 2936, 1638, 1397 cm^{-1}; $[\alpha]_D^{25}$: +183.5 (C 1.0, $CHCl_3$); HRMS (ESI): Calcd for $C_7H_{10}O_3Na$ $[M + Na]^+$ 165.0528, found 165.0528.

(R,Z)-2-(3-ethylidene-3,4-dihydro-2H-pyran-4-yl)acetaldehyde (**19**). To a solution of compound **18** (0.32 g, 2.44 mmol) in anhydrous CH_2Cl_2 (20 mL) were added $NaHCO_3$ (2.08 g, 24.76 mmol) and Dess-Martin periodinane (1.56 g, 3.68 mmol) respectively. The reaction mixture was allowed to stir until completion of the reaction (20 min). The reaction was quenched by adding water (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with

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brine (2 × 10 mL), water (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude ketone derivative, which was carried out without further purification as the obtained ketone was found to be very unstable. The crude ketone derivative in anhydrous THF (4 mL) was added to the ylide (generated by using ethyltriphenylphosphonium bromide (3 equiv) and *n*-BuLi (2.8 eq) at 0 °C in THF (10 mL)) at -78 °C. The reaction mixture was allowed to reach 25 °C and stirred until completion of the reaction (12 h). The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) at 0 °C. The mixture was extracted with ethyl acetate (3 × 20 mL) and washed with brine (2 × 20 mL), water (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product, which was carried out without further purification as the obtained product was also found to be very unstable. The above obtained crude derivative in nitrobenzene (8 mL) and *N,N*-dimethylaniline (0.2 mL) was heated at 160 °C until completion of the reaction (3 h). The reaction mixture was directly loaded over the silica-gel and purified using hexanes and ethyl acetate to obtain pure compound **19** (0.2 g, 65% over three steps) as a light yellow oil. R_f = 0.25 (EtOAc/Hexanes, 5%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1H), 6.38 (d, *J* = 6.0 Hz, 1H), 5.59 (q, *J* = 6.4 Hz, 1H), 4.68 (bs, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 3.21 (bs, 1H), 2.54 (t, *J* = 7.2 Hz, 2H), 1.66 (d, *J* = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 144.4, 132.5, 122.6, 103.5, 61.6, 50.5, 33.3, 12.7; IR (neat): ν_{max} = 3063, 2854, 1726, 1643, 1463 cm^{-1}; HRMS (ESI): Calcd for $C_9H_{12}O_2Na$ $[M + Na]^+$ 175.0735, found 175.0730.

(R,Z)-2-(3-Ethylidene-3,4-dihydro-2H-pyran-4-yl)ethanol (**20**). To a solution of compound **19** (0.12 g, 0.78 mmol) in absolute EtOH (5 mL) was added $NaBH_4$ (0.05 g, 1.42 mmol) at 0 °C and the reaction mixture was stirred until completion of the reaction (10 min). Saturated aqueous NH_4Cl solution (1 mL) was added at the same temperature. The observed precipitate was filtered through a short Celite® 545 plug and the filtrate was concentrated under reduced pressure to obtain crude alcohol derivative. The crude product was purified over silica-gel using hexanes and ethyl acetate to obtain compound **20** (0.11 g, 96 %) as a colourless oil. R_f = 0.60 (EtOAc/Hexanes, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (d, *J* = 6.0 Hz, 1H), 5.56 (q, *J* = 6.8 Hz, 1H), 4.71 (bs, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 11.6 Hz, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.69 (bd, *J* = 3.6 Hz, 1H), 1.87 (bs, 1H), 1.75-1.69 (m, 1H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.64-1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 133.6, 121.7, 104.8, 61.2, 60.1, 39.7, 35.6, 12.7; IR (neat): ν_{max} = 3380, 2920, 1643, 1561 cm^{-1}; $[\alpha]_D^{25}$: -258.2 (C 0.57, $CHCl_3$); HRMS (ESI): Calcd for $C_9H_{15}O_2$ $[M + H]^+$ 155.1072, found 155.1070.

(1R,5R,Z)-4-Ethylidene-2,8-dioxabicyclo[3.3.1]nonane (Isoneosemburin, (**21**)). To a solution of compound **20** (0.1 g, 0.64 mmol) in anhydrous CH_2Cl_2 (10 mL) under inert atmosphere was added powdered 4 Å molecular sieves and cooled to 0 °C. To the above solution, freshly distilled TMSOTf (0.02 g, 15 mol %) was added and the reaction mixture was stirred until completion of the reaction (1 h). The reaction was slowly quenched with Et_3N at 0 °C and the temperature was allowed to reach 25 °C. The reaction mixture was filtered and concentrated under reduced pressure. The crude obtained was purified by column chromatography over silica-gel using hexanes and ethyl acetate to give compound **21** (85 mg, 85%) as a colourless oil. R_f = 0.60 (EtOAc/Hexanes, 20%); ^{1}H NMR (400 MHz, C_6D_6): δ = 5.48 (s, 1H), 5.09, (q, *J* = 6.0 Hz, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 4.21-4.12 (m, 2H), 3.60 (dd, *J* = 5.2, 10.8 Hz, 1H), 2.38 (bs, 1H), 1.88-1.79 (m, 1H), 1.62 (s, 2H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.27 (bd, *J* = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 139.1, 118.7, 92.8, 62.0, 57.2, 34.6, 30.6, 29.6, 12.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34-5.28 (m, 2H), 4.67 (d, *J* = 14.8 Hz, 1H), 4.22 (d, *J* = 14.8 Hz, 1H), 3.99 (dt, *J* = 3.2, 12.4 Hz, 1H), 3.55 (dd, *J* = 5.6, 11.6 Hz, 1H), 2.66 (bs, 1H), 2.04-1.96 (m, 1H), 1.91-1.81 (m, 2H), 1.57 (d, *J* = 8.5 Hz, 3H), 1.46 (bd, *J* = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 119.5, 92.9, 62.3, 57.4, 34.4, 29.9, 29.4, 12.5; IR (neat): ν_{max} = 3424, 2931, 2882, 1561, 1441 cm^{-1}; $[\alpha]_D^{25}$: -32.4 (C 1.0, $CHCl_3$); HRMS (ESI): Calcd for $C_9H_{15}O_2$ $[M + H]^+$ 155.1072, found 155.1067.

2-((4R,5S)-5-Acetoxy-2-methoxytetrahydro-2H-pyran-4-yl)ethyl acetate (**24**). To a solution of compound **5** (2.2 g, 11.68 mmol) in anhydrous pyridine (30 mL) under inert atmosphere was added acetic anhydride (5.90 mL, 58.44 mmol) at 0 °C. The reaction was allowed to reach 25 °C and the reaction mixture was stirred until completion (4 h). Pyridine was completely removed under reduced pressure and the crude product was purified over silica-gel using hexanes and ethyl acetate to obtain diacetate derivative (2.56 g, 96%) as colourless oil. R_f = 0.70 (EtOAc/Hexanes, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (dd, *J* = 1.6, 6.4 Hz, 1H), 4.84-4.81 (m, 1H), 4.67 (ddd, *J* = 0.8, 3.2, 7.2 Hz, 1H), 4.16-4.12 (m, 2H), 3.89-3.88 (m, 2H), 2.27-2.23 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.83-1.74 (m, 1H), 1.63-1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.4, 143.6, 101.2, 69.7, 63.9, 61.5, 33.7, 32.6, 21.1, 20.9; IR (neat): ν_{max} = 2974, 2871, 1736, 1643, 1639 cm^{-1}; $[\alpha]_D^{25}$: -119.2 (C 1.0, $CHCl_3$); HRMS (ESI): Calcd for $C_{11}H_{16}O_5Na$ $[M + Na]^+$ 251.0896, found 251.0897. To a stirred solution of the above diacetylated derivative (2.0 g, 8.8 mmol) in anhydrous CH_3CN (100 mL) under inert atmosphere was added LiBr (1.52 g, 17.6 mmol), MeOH (0.7 mL) and Dowex® 50WX4 (2.16 g) respectively, at 0 °C. The temperature was slowly allowed to reach 25 °C and stirring was continued until completion of the reaction (1 h). The mixture was filtered through Celite® 545 plug and the filtrate was taken into ethyl acetate (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL). The aqueous layer was further extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography over silica-gel using hexanes and ethyl acetate provided **24** (1.8 g, 80%) as a colourless oil and the β-isomer in 14% yield. R_f = 0.80 (EtOAc/ Hexanes, 30%); (For α-isomer)^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64 (bd, *J* = 1.6 Hz, 1H), 4.62 (dd, *J* = 5.2, 10.4 Hz, 1H), 4.11-4.00 (m, 2H), 3.69 (dd, *J* = 5.2, 10.8 Hz, 1H), 3.47 (t, *J* = 10.0 Hz, 1H), 3.33 (s, 3H), 2.16-2.09 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.96-1.91 (m, 1H), 1.87-1.79 (m, 1H), 1.50-1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.4, 97.0, 71.7, 61.9, 59.8, 54.6, 34.4, 31.6, 30.9, 20.9, 20.9; IR (neat): ν_{max} = 3052, 2926, 2854, 1736, 1435 cm^{-1}; HRMS (ESI): Calcd for $C_{12}H_{20}O_6Na$ $[M + Na]^+$ 283.1158, found 283.1162.

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(3S,4R,6S)-4-(2-(tert-Butyldimethylsilyloxy)ethyl)-6-methoxytetrahydro-2H-pyran-3-ol (**25**). To a solution of compound **24** (1.53 g, 5.85 mmol) in anhydrous MeOH (30 mL) under inert atmosphere was added K_2CO_3 (8.1 mg) and the reaction mixture was stirred until completion of the reaction (3 h). MeOH was evaporated under reduced pressure and the obtained crude diol was dissolved in anhydrous DMF (6 mL). Imidazole (0.78 g, 11.73 mmol) and TBSCl (0.87 g, 5.85 mmol) were added at 0 °C under inert atmosphere and the mixture was stirred at 25 °C until completion of the reaction (5 h). DMF was completely evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate. The organic solution was washed with water (2 × 20 mL), brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. Removal of ethyl acetate under reduced pressure followed by purification of crude product over silica-gel using hexanes and ethyl acetate provided compound **25** (1.35 g, 85% for two steps) as a colourless oil. R_f = 0.70 (EtOAc/Hexanes, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (bs, 1H), 4.62 (dd, *J* = 2.0, 3.2 Hz, 1H), 3.83-3.78 (m, 1H), 3.71-3.62 (m, 2H), 3.45 (t, *J* = 10.4, Hz, 1H), 3.3 (s, 3H), 1.87-1.79 (m, 1H), 1.75 (dd, *J* = 4.0, 13.6 Hz, 1H), 1.57-1.42 (m, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.2, 70.5, 63.1, 62.7, 54.4, 38.5, 37.9, 36.3, 25.8, 18.2, -5.4, -5.5; IR (neat): ν_{max} = 3408, 2926, 2882, 1473, 1435 cm^{-1}; $[\alpha]_D^{25}$: +64.4 (C 0.27, $CHCl_3$); HRMS (ESI): Calcd for $C_{14}H_{30}O_4SiNa$ $[M + Na]^+$ 313.1811, found 313.1810.

(S)-4-(2-(tert-Butyldimethylsilyloxy)ethyl)-6-methoxydihydro-2H-pyran-3(4H)-one (**26**). To a solution of compound **25** (1.0 g, 3.44 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (DMP) (1.75 g, 4.1 mmol). The reaction mixture was allowed to stir until completion of the reaction (20 min). The reaction was quenched by adding water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), water (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude ketone derivative. The crude was purified over silica-gel using hexanes and ethyl acetate to obtain compound **26** (0.93 g, 94%) as a colourless oil. R_f = 0.50 (EtOAc/Hexanes, 15%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.93 (t, *J* = 6.5 Hz, 0.5H), 4.80 (t, *J* = 3.0 Hz, 0.5H), 4.13 (d, *J* = 7.5 Hz, 0.5H), 4.09 (d, *J* = 5.5 Hz, 0.5H), 3.89-3.82 (m, 1H), 3.65-3.61 (m, 2H), 3.40 (s, 1.5H), 3.36 (s, 1.5H), 2.90-2.84 (m, 0.5 H), 2.73-2.67 (m, 0.5H), 2.50-2.45 (m, 0.5H), 2.21-2.17 (m, 0.5H), 2.10-2.01 (m, 1H), 1.88-1.82 (m, 0.5H), 1.51-1.31 (m, 1.5H), 0.83 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 208.6, 98.7, 97.5, 67.3, 66.4, 60.3, 55.3, 55.2, 39.7, 39.3, 35.2, 33.2, 31.6, 30.5, 25.8, 18.2, -5.4; IR (neat): ν_{max} = 2958, 2931, 2854, 1731, 1468 cm^{-1}; $[\alpha]_D^{25}$: +126.9 (C 1.0, $CHCl_3$); HRMS (ESI): Calcd for $C_{14}H_{28}O_4SiNa$ $[M + Na]^+$ 311.1655, found 311.1651.

(3aR,5S,7aR)-5-Methoxyhexahydro-2H-furo[2,3-c]pyran-7a-ol (**28**). To a solution of compound **26** (0.37 g, 1.28 mmol) in anhydrous THF (10 mL) was added TBAF (1.92 mL, 1 M solution in THF) and the mixture was stirred at room temperature until completion of the reaction (2 h). Saturated aqueous NH_4Cl solution (5 mL) was added and the obtained mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified over silica-gel using hexanes and ethyl acetate provided compound **28** (0.21 g, 95%) as a colourless oil. R_f = 0.20 (EtOAc/Hexanes, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.66 (bs, 1H), 4.12-4.01 (m, 2H), 3.77 (d, *J* = 12.0 Hz, 1H), 3.63 (d, *J* = 12.0 Hz, 1H), 3.36 (s, 3H), 2.43-2.37 (m, 2H), 1.81-1.76 (m, 1H), 1.62-1.56 (m, 1H), 1.50-1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.89, 97.2, 66.3, 61.9, 54.9, 36.9, 32.2, 29.4; IR (neat): ν_{max} = 3397, 2893, 2832, 1726, 1446 cm^{-1}; $[\alpha]_D^{25}$: +141.5 (C 0.78, $CHCl_3$); HRMS (ESI): Calcd for $C_8H_{14}O_4Na$ $[M + Na]^+$ 197.0790, found 197.0794.

2-((2S,4R,E)-5-Ethylidene-2-methoxytetrahydro-2H-pyran-4-yl)ethanol (**22**). To a solution of ethyltriphenylphosphonium bromide (1.38 g, 3.72 mmol) in dry THF (10 mL) was slowly added *n*-BuLi (2.5 M solution in hexanes, 1.34 mL, 3.34 mmol) at 0 °C and stirring was continued over a period of 1 h at the same temperature under inert atmosphere. To the above generated ylide, compound **28** (0.13 g, 0.74 mmol) in anhydrous THF (10 mL) was added slowly at -78 °C and the reaction mixture was stirred until completion of the reaction (12 h) at 25 °C. The reaction was cooled to 10 °C and quenched by drop wise addition of saturated aqueous NH_4Cl solution (2 mL). The mixture was diluted with hexanes and filtered through Celite® 545 plug and concentrated under reduced pressure. The crude was purified by column chromatography over silica-gel using hexanes and ethyl acetate to obtain compound **22** (0.12 g, 90%) as a colourless oil. R_f = 0.25 (EtOAc/Hexanes, 40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (q, *J* = 6.8 Hz, 1H), 4.65 (dd, *J* = 2.8, 9.2 Hz, 1H), 4.18-4.02 (m, 2H), 3.68-3.57 (m, 2H), 3.44 (s, 3H), 3.01-2.98 (m, 1H), 1.90-1.80 (m, 2H), 1.79-1.66 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.54-1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 120.8, 99.5, 67.5, 60.9, 55.9, 35.9, 29.6, 29.6, 12.7; IR (neat): ν_{max} = 3413, 2931, 2865, 1446, 1397 cm^{-1}; $[\alpha]_D^{25}$: +59.6 (C 1.0, $CHCl_3$); HRMS (ESI): Calcd for $C_{10}H_{18}O_3Na$ $[M + Na]^+$ 209.1154, found 209.1150.

(1R,5R,E)-4-Ethylidene-2,8-dioxabicyclo[3.3.1]nonane (Neosemburin, (**3**)). To a solution of compound **22** (70 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (10 mL) under inert atmosphere was added powdered 4 Å molecular sieves and cooled to 0 °C. To the above solution, freshly distilled TMSOTf (15 mol %) was added and the reaction mixture was stirred until completion of the reaction (1 h). The reaction was slowly quenched with Et_3N at 0 °C and was allowed to reach 25 °C. The reaction mixture was filtered and concentrated under reduced pressure. The crude was purified by column chromatography over silica-gel using hexanes and ethyl acetate to obtain compound **3** (60 mg, 90%) as a colourless oil. R_f = 0.65 (EtOAc/Hexanes, 30%); ^{1}H NMR (400 MHz, C_6D_6): δ = 5.42 (bs, 1H), 5.08-5.03 (m, 1H), 4.12 (dt, *J* = 2.8, 14.4 Hz, 1H), 4.07 (bs, 2H), 3.48 (dd, *J* = 5.2, 11.2 Hz, 1H), 2.47 (s, 1H), 1.63-1.58 (m, 1H), 1.48-1.47 (m, 2H), 1.29-1.27 (m, 3H), 1.21 (bd, *J* = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 139.5, 118.6, 93.5, 67.3, 57.0, 31.7, 29.2, 26.3, 12.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (q, *J* = 6.8 Hz, 1H), 5.37 (bs, 1H), 4.32-4.28 (m, 1H), 4.21-4.17 (m, 1H), 4.03 (dt, *J* = 3.2, 13.2 Hz,

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1H), 3.56 (dd, *J* = 5.6, 11.6 Hz, 1H), 2.97 (bs, 1H), 2.00-1.96 (m, 1H), 1.95-1.90 (m, 1H), 1.89-1.87 (m, 1H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.56 (bd, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 119.3, 93.4, 67.4, 57.1, 31.3, 28.9, 25.8, 12.6; IR (neat): ν_{max} = 3419, 2926, 2849, 1726, 1621, 1446 cm^{-1}; $[\alpha]_D^{25}$: +7.5 (C 0.06, $CHCl_3$); HRMS (ESI): Calcd for $C_9H_{15}O_2$ $[M + H]^+$ 155.1072, found 155.1070.

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Notes and references

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† Electronic Supplementary Information (ESI) available: ^{1}H, ^{13}C and DEPT spectra of all new compounds and 2D spectra, ^{1}H -^{1}H COSY and ^{1}H - ^{1}H NOESY, of bicyclic compounds **3**, **21** and **28**. A ^{1}H NMR data comparision table for isolated and synthesized neosemburin. See DOI: 10.1039/b000000x/

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18 The authors in the original paper (reference 5) mistakenly assigned the geometry of the olefin as *Z* while in the structure they provided it was found to be the *E* olefin.

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