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ARTICLE TYPE

A stereocontrolled synthesis of Hagen's gland lactones via iterative proline catalyzed α-aminoxylation and oxa-Michael addition reactions

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A simple and efficient synthesis of Hagen's gland lactones was achieved using a sequential α-aminoxylation/oxa-Michael approach in a highly diastereoselective manner with assignment of relative configurations. This method was found to be applicable for the synthesis of various other isomers of Hagen's gland lactones.

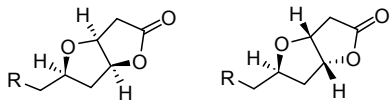
Introduction

Hagen's glands (Fig. 1) earlier known as pygidialglands (located near the abdominal tips) of the braconid wasps, D. Longicaudata (Ashmead), D. Tryoni (Cameron) and Fopius (Biosteres) arisanus, are found to contain fragrance rich lactones. This was first observed by Hagen (1953) and Buckingham (1975) who also put in efforts to study the significance of these secretions in the pest management of fruitfly population control in Hawaii and eastern Queensland, especially against the Queensland fruitfly. Bactroceratryoni which is known to be an aggressive pest with a wide host range.[1] Williams *et al*. suggested the presence of two bicyclic lactones and experimentally characterized these bicyclic lactones by NMR studies using Karplus based calculations.[1c] Kitching *et al*. have determined the absolute stereochemistry of these lactones through synthesis which employs an interesting route that uses 1,3-diol approach followed by $PdCl_2$-catalyzed oxy carbonylation − lactonization reaction.[2a]

Considering their possible role in pest management strategies, several authors have reported the synthesis of these lactones either targeting the natural isomer or its epimer. Chiral pool approaches have been employed for the synthesis of Hagens gland lactones from carbohydrates, [3,4] chiral glycidols,[5] and lactones derived from carbohydrates such as mannofuranolactone[6] and D-glucono-δ-lactone. [7a,b] Very recently, Lepore *et al.* described an enantioselective synthesis of Hagen`s gland lactones from 2,3-allenols.[7c] In yet another report Gharpure *et al.* made use of synthetic intermediates like cyclopropanes (DAC) for the synthesis of target lactones.[8]

During last decade, there has been growing interest in the use of small organic molecules to catalyze reactions in a stereoselective manner in organic synthesis. Proline is among the most successful secondary amine based organocatalysts which have been widely employed in several organic transformations.[9]

As a part of our research interest in developing new methodolo gies and their subsequent application to bioactive compounds,[10] we have recently developed an iterative approach to enantiopure synthesis of *syn* and *anti*-1,3-polyols based on proline catalyzed



1 R = *n* - C_3H_7 **2** R = *n* - C_3H_7
3 R = *n* - C_5H_{11} **4** R = *n* - C_5H_{11}

Figure 1. Hagen's gland lactones (**2** & **4**) and their epimers (**1** & **3**).

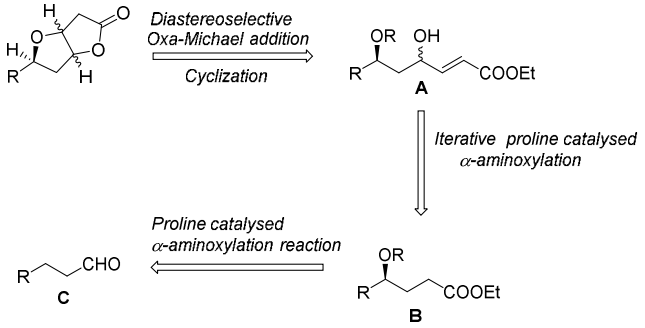
sequential α-aminoxylation, followed by Horner-Wadsworth-Emmons olefination of aldehydes at ambient temperature.[11a] This method has several advantages over the most widely used method to prepare 1,3-polyols in an iterative fashion. We have earlier reported the synthesis of various lactones using 1,3-polyol approach.[11b] However the construction of bridged framework containing THF ring systems using the same remains unexplored. We now report the application of this methodology along with a highly diastereoselctive oxa-Michael addition reaction in the efficient synthesis of substituted tetrahydrofuro [3,2-b]furan-2(3*H*)-one derivatives (Hagen's gland lactones).

Results and Discussion

As per the retrosynthetic scheme as delineated in Scheme 1, the Hagen's gland lactones could be synthesized from the skipped 1,3-diol fragment **A**. We envisioned that **A** could be derived from γ–hydroxy ester moiety **B**, a common intermediate which in turn could be obtained via iterative sequential α-aminoxylation and Horner-Wadsworth- Emmons olefination of aldehyde **C**.

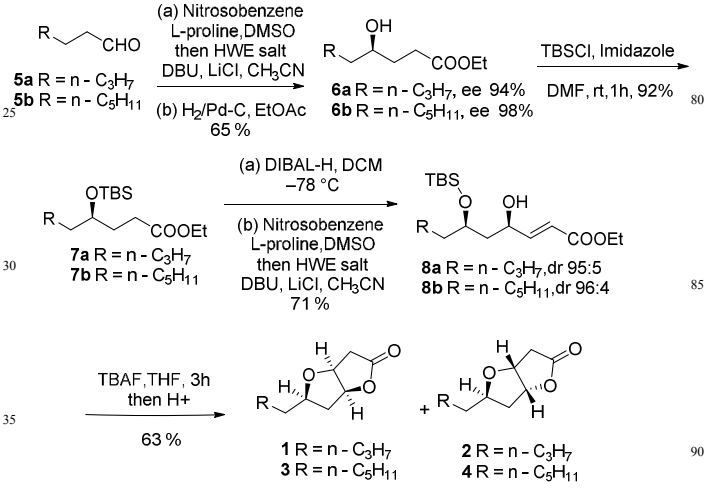
As shown in scheme 2, the synthesis of the target lactones commenced with the commercially available hexanal **5a** which on sequential α-aminoxylation using nitroso benzene as the oxygen source and L-proline as catalyst and subsequent HWE olefination using triethylphosphonoacetate, followed by hydrogenation using a catalytic amount of Pd/C, furnished the γ–hydroxy ester **6a**. Thus, in two steps and one column purification **6a** was obtained in 65% yield and 94% ee.[11c] Similarly compound **6b** was obtained from **5b** in 65% yield and

98% ee. Protection of the free hydroxyl group of **6a&6b** as its TBS ether gave **7a&7b** in 92% yield respectively. The TBS protected hydroxyester **7a** was then reduced using DIBAL-H in toluene at -78 ^{o}C to furnish an aldehyde.



Scheme 1. Retrosynthetic route to the synthesis of Hagen's gland lactones

Crude aldehyde was further subjected to α-aminoxylation reaction using L-proline as a catalyst followed by HWE-olefination to yield *syn* TBS protected γ-hydroxy ester **8a** in good diastereomeric excess (dr ratio 95:5).[12] Using the same procedure **8b** was obtained from **7b** in 71% yield (dr ratio 96:4). With *syn*-1,3-diol **8a** in hand we proceeded to the synthesis of Hagen's gland lactones using oxa-Michael addition The key steps involved the fluoride-mediated cleavage of a silyl protecting group using TBAF in THF followed by lactonisation with catalytic amount of HCl (pH~3 in toluene). At this stage we could observe the formation of two products **1** & **2** (ratio 5:1).[13] In a similar way compounds **3** and **4** were obtained from **8b** using oxa-Michael addition followed by lactonization.



Scheme 2.Synthesis of Hagen's gland Lactones

Taking into consideration this observation we considered it worthwhile to study the stereochemistry of both the products which was confirmed using detailed 1D and 2D-NMR techniques.

For compound **1**, proton H_{3a} shows nOe correlation with proton H_{6a} indicating syn stereochemistry at the bridgehead of the substituted tetrahydrofuro[3,2-b]furan-2(3H)-one. H_{3a} also shows nOe correlation with proton H_5, which confirms the *syn* relative stereochemistry between these three protons as shown in the pictorial representation of the compound in the Figure 2. (see Supporting information for spectra)

In case of compound **2**, the H_5 proton shows nOe correlation with $H_{6\alpha'}$ while H_{6a} shows nOe correlation with $H_{6\beta'}$. These results show that the H_{6a} and H_5 methine protons show nOe correlation with different protons of the furyl methylene indicating anti relative stereochemistry between H_5 and H_{6a} as shown in the pictorial representation in Figure 2. (see SI for spectra).

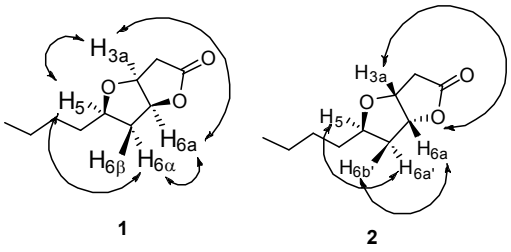
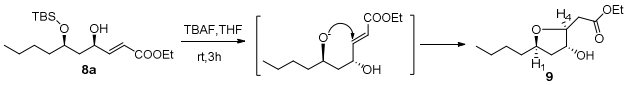


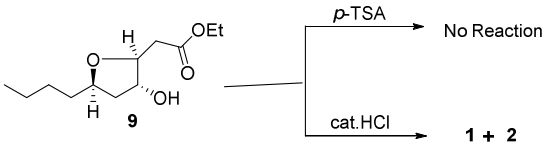
Figure 2: Pictorial representation of both cis and trans nOe correlations

This result motivated us to study the stereoselection of both oxa-Michael and cyclization reactions very closely. The reproducibility of the strategy and high yielding steps efficiently allowed us to quickly synthesize 1,3-syn diol **8a** which was subjected to simultaneous desilylation/oxa-Michael reaction. Instead of going further for cyclization at this stage, we quenched the reaction mixture using saturated ammonium chloride solution to get the oxa-Michael product **9** (scheme 3). Preliminary examination using Thin Layer Chromatography showed the presence of only one product. ^{1}H and ^{13}C NMR (see supporting information) did not show the formation of other diastereomer and revealed that the oxa-Michael addition reaction proceeded in a highly diastereoselective manner. The stereochemistry of compound **9** was confirmed using detailed 1D and 2D NMR techniques. (see SI for spectra)



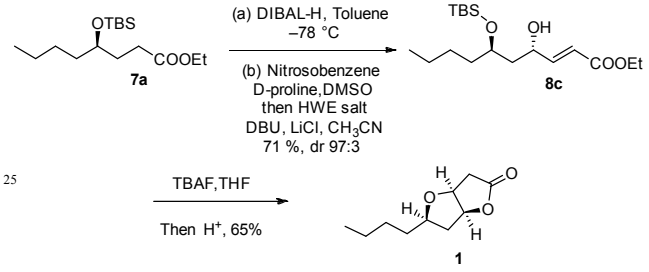
Scheme 3: Diastereoselective oxa-Michael addition reaction of **8a**

It was observed that in compound **9**, H_4 and H_1 shows nOe correlations indicating syn relative stereochemistry[14] while none of them shows nOe correlations with H_3 indicating anti relative stereochemistry with H_3 as shown in the pictorial representation in Figure 3. The possible reason for the formation of mixture of diastereomers in the cyclization step could be attributed to the epimerisation of either of the two protons (H_3 or H_4) in the presence of HCl (P^{H}~3) under reflux conditions, leading to cyclization with both the ring junction protons syn to each other. To prevent the racemization and to check the feasibility of cyclization of **9** without epimerisation, we further carried out reaction using *p*-TSA in toluene both at room temperature and under reflux conditions. As anticipated, the cyclization reaction proved to be a total failure as it gave only the starting material back (scheme 4).



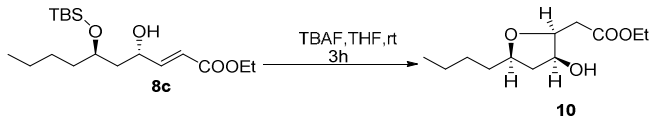
Scheme 4: Lactonisation reaction

In order to rationalise our findings, we planned to test the devised strategy by synthesizing 1,3-anti diol as an intermediate. For this purpose, we started with previously synthesized protected γ-hydroxy ester **7a** which was reduced using DIBAL-H in toluene at -78 ^{o}C to furnish corresponding aldehyde. Crude aldehyde was further subjected to α-aminoxylation/HWE olefination reaction using D-proline as a catalyst to obtain 1,3-anti diol **8c** with an excellent dr ratio (97:3).[13] To test the formation of diastereomeric mixture one-pot oxa Michael/ lactonization was performed on the diol. In this case we observed the formation of only one product as characterised by ^{13}C-NMR which was an entirely different result when compared to the *syn*-diol product (Scheme 5).



Scheme 5: Synthesis of *epi*-Hagen's gland lactone

This observation was further substantiated and proved by isolating compound **10** and examining the course of reaction by its treatment under various acidic conditions. Towards this end, compound **8c** was subjected to a concomitant desilylation and oxa-Michael with TBAF in THF for 3h to obtain **10** in 85% as shown in scheme 6. Characterisation of the oxa-Michael adduct **10** was carried out by 1D and 2D NMR techniques.



Scheme 6: Synthesis of compound **10**

For compound **10**, H_3 proton shows nOe correlation with both methine protons H_1 and H_4 indicating *syn* stereochemistry among them. The relative stereochemistry was also confirmed with the help of methylene group which shows two different signals for two protons (H_2 and H_5). The H_1 and H_3 methine protons show nOe correlations only with H_2 proton, but it does not show any correlation with H_5 proton indicating all the three methine protons (H_1, H_3 and H_4) being syn to each other as shown in the pictorial representation in figure 3.

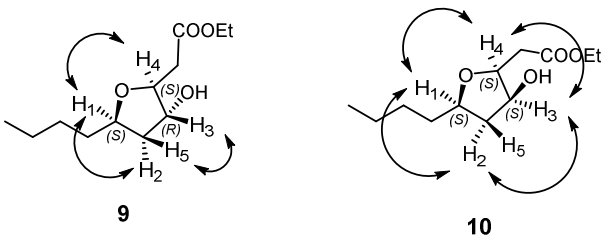
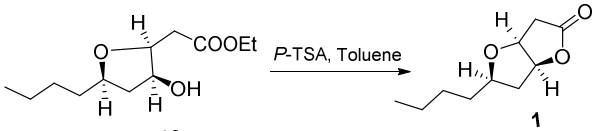


Figure 3: nOe correlations for compounds **9** and **10**

After confirming the stereochemistry of compound **10**, it was initially subjected to cyclization using *p*-TSA at rt to give compound **1** as sole product. We then examined the epimerisation using reflux conditions in the presence of *p*-TSA, when no epimerisation occurred we then tried using conc. HCl at both rt and under reflux conditions. Interestingly, no epimerisation was observed and cyclization was smooth leading to the desired product **1** in excellent yield.



Scheme 7: Lactonisation reaction

This could be due to the syn stereochemistry of the intermediate making cyclisation more facile than the epimerisation at C-3 centre. To check the reproducibility and improve the confidence in the stereochemical outcome by the above methods, we thought of extrapolating the strategy to the synthesis of **3** and **4** isolated from *D.krausii*. Both the compounds could easily be synthesized to obtain a separable mixture of cis and trans isomers from the corresponding aldehyde octanal **5b** by subjecting it to similar set of reaction conditions as described in scheme 2. Thus, epi-Hagen`s gland lactone **1** was obtained in overall ~28% yield and Hagen`s gland lactone **2** in ~ 4.5% yield starting from cheap and easily available aldehydes in 4 steps only.

Conclusions

In conclusion, we have developed a new, efficient and organocatalytic protocol to Hagens gland lactones using a proline catalyzed α- aminoxylation and consequent oxa-Michael reactions. We believe that this approach would permit maximum variability in the product structure and can be extended to the synthesis of other stereoisomers and synthetic analogues. The synthesis reported uses mild reaction conditions (at room temperature, air and moisture are tolerated), both enantiopure forms of proline are commercially available, Thus by using the suitable catalyst, desirable stereocenters can be obtained (highly stereo divergent). A short reaction sequence with a stereochemical assignment has made this approach amenable to similar natural products. Currently, studies are in progress toward this goal.

Acknowledgements

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Experimental section

Ethyl (*R*)-4-hydroxydecanoate (6b):General procedure for α-aminoxylation:To a solution of octanal (2.0 g, 15.62 mmol) and nitroso benzene (1.6 g, 15.62 mmol) in anhydrous DMSO (29 mL) was added L-proline (0.72 g, 6.2 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (6.22mL, 31.25 mmol), DBU (4.29 mL, 31.25 mmol) and LiCl (1.32 g, 31.25 mmol) in CH_3CN (29 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give γ-alcohol. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (85:15) as eluent to give ethyl (*R*)-4-hydroxydecanoate **6b** as a colourless liquid(2.19 g, yield 65%).$[\alpha]_D^{25}$: +1.17 (c 1.5, $CHCl_3$), IR ($CHCl_3$, cm-1): ν^{max} 3432, 2934, 1718. ^{1}H NMR (200MHz, $CDCl_3$) δ 4.13 (q, J = 7.2 Hz, 2H), 3.67-3.52 (m, 1H), 2.50-2.39 (m, 2H), 1.99-1.61 (m, 4H), 1.56-1.29 (m, 8H), 1.29-1.22 (m, 3H), 0.92 (d, J = 4.8 Hz, 3H) ppm.^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 80.9, 71.0, 60.2, 37.4, 32.1, 30.7, 29.5, 25.5, 22.5, 14.0, 13.9 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{24}O_3Na$ 239.1618; Found 239.1614 HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : petroleum ether = 10:90, flow rate 0.5ml/min. Retention time (min):78.483 (minor) and 80.708 (major).The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee>98%.

Ethyl (*R*)-4-((tert-butyldimethylsilyl)oxy)decanoate (7b):To an ice-cold stirred solution of **6b** (1.70 g, 7.87 mmol) in DMF (10 mL) were added imidazole (1.00 g, 15.74 mmol) and TBSCl (1.77g, 11.80 mmol) at 0 °C. The resulting mixture was stirred for 1 h at rt before H_2O (20 mL) was added. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography using petroleum ether: ethyl acetate: (95:05) of the crude product gave TBS ether **7b** as a colorless liquid(2.39 g, yield 92%).$[\alpha]_D^{25}$: -7.08 (*c* 1.6, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 2856, 1726. ^{1}H NMR (200MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 3.75-3.59 (m, 1H), 2.40-2.29 (m, 2H), 1.82-1.63 (m, 2H), 1.47-1.34 (m, 2H), 1.30-1.22 (m, 11H), 0.88 (m, 12H), 0.04 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 71.2, 60.2, 37.0, 31.8, 31.7, 30.1, 29.5, 25.9, 25.1, 22.6, 18.1, 14.2, 14.1, -4.4, -4.6 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{38}O_3NaSi$ 353.2482; Found 353.2472

Ethyl (4*R*,6*R*,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (8a):To a solution of ethyl ester **7a** (1.0 g, 4.63mmol) in CH_2Cl_2 (6 mL), was added DIBAL-H (2.5 mL 2.3 M solution in toluene, 5.09mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (2.5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colourless liquid, which was directly used in the next step without further purification. Following the general procedure for α-aminoxylation (L-proline as a catalyst) **8a** was obtained as a crude product (~95% diastereomeric excess) and was purified by flash column chromatography using petroleum ether:ethyl acetate (9:1) to furnish pure diol **8a** as a colorless liquid(0.80 g, yield 71%).$[\alpha]_D^{25}$:- 15.76 (*c* 0.6, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max}3436, 2967, 1218. ^{1}H NMR (200MHz, $CDCl_3$) δ 6.92 (dd, J = 4.4, 15.6 Hz, 1H), 6.10 (dd, J= 1.8, 15.6 Hz, 1H), 4.46 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.96 (m, 1H), 1.76-1.50 (m, 4H), 1.27-1.23 (m, 7H), 0.94-0.90 (m, 12H), 0.16-0.08 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 149.7, 119.8, 73.3, 70.4, 60.3, 41.9, 37.7, 26.8, 25.8, 22.8, 17.9, 14.2, 14.0, -4.0, -4.8 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{36}O_4NaSi$ 367.2275; Found 367.2275.

HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H_2O = 90:10), flow rate 1.0ml/min,(λ = 210 nm). Retention time (min): 7.31 (major) and 7.89 (minor),(dr 95:5)

Ethyl (4*S*,6*R*,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (8c):The above procedure was followed using D-Proline as a catalyst (0.79 g, yield 70%)$[\alpha]_D^{25}$: -7.5 (*c* 0.4, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 3430, 2934, 1718. ^{1}H NMR (200MHz, $CDCl_3$) δ 6.92 (dd, J = 4.2, 15.6 Hz, 1H), 6.11 (dd, J = 1.9, 15.5 Hz, 1H), 4.64 (dtd, J = 1.8, 4.2, 8.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.05-3.94 (m, 1H), 1.74-1.65 (m, 2H), 1.29 (t, J = 7.1 Hz, 9H), 0.90 (m, 12H), 0.09 (d, J = 1.4 Hz, 6H) ppm.^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 150.4, 119.8, 71.5, 68.0, 60.3, 40.5, 35.7, 27.8, 25.8, 22.7, 17.9, 14.2, 14.0, -4.5, -4.8 ppm. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{18}H_{36}O_4NaSi$ 367.2273; Found 367.2275.

HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H_2O = 90:10), flow rate 1.0 ml/min,(λ = 210 nm). Retention time (min): 6.91 (major) and 7.43 (minor),dr3:97

Ethyl (4*R*,6*R*,E)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydodec-2-enoate (8b):(0.80 g, yield 70%)$[\alpha]_D^{25}$: -6.49 (*c* 1.8, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 3450, 2920. ^{1}H NMR (200MHz, $CDCl_3$) δ 6.91 (dd, J = 4.4, 15.6 Hz, 1H), 6.10 (dd, J = 1.9, 15.5 Hz, 1H), 4.24 - 4.09 (m, 2H), 4.07-3.82 (m, 1H), 3.82-3.51 (m, 1H), 1.63-1.52 (m, 4H), 1.27 (d, J = 4.5 Hz, 11H), 0.92-0.88 (m, 12H), 0.12 (d, J = 2.5 Hz, 6H) ppm.^{13}C NMR (126

MHz, $CDCl_3$) δ 166.7, 149.7, 119.8, 73.3, 70.4, 60.3, 42.0, 38.0, 31.8, 29.4, 25.8, 24.6, 22.5, 17.9, 14.2, 14.0, -4.0,-4.7 ppm. HRMS (ESI) m/z:[M + Na]+ Calcd for $C_{20}H_{40}O_4NaSi$ 395.2588; Found 395.2578.

HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H_2O = 90:10), flow rate 1.0 ml/min,(λ = 210 nm). Retention time (min):10.61(major) and 11.61 (minor), dr 96:4.

Ethyl 2-((2*S*,3*R*,5*R*)-5-butyl-3-hydroxytetrahydrofuran-2-yl)acetate (9):The solution of **8a** (0.25 g, 0.92 mmol) was treated with TBAF (0.5 mL, 1.8 mmol) in THF (3 mL) at 0 ^oC. The reaction mixture was stirred for 3 h and quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give a crude product. Silica gel column chromatography using petroleum ether: ethyl acetate: (8:2) of the crude product gave oxa-Michael product **9** as a colorless liquid(0.14 g, yield 85%).

$[\alpha]_D^{25}$: +1.3 (*c* 0.3, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 3463, 2931, 1764. ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, *J* = 7.0 Hz, 2H), 4.14-4.10 (m, 1H), 4.06 (dd, *J* = 6.1, 9.2 Hz, 1H), 3.95 (td, *J* = 4.6, 9.4 Hz, 1H), 2.80 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.51 (dd, *J* = 9.2, 16.5 Hz, 1H), 2.35 (t, *J* = 7.6 Hz, 1H), 2.01-1.96 (m, 1H), 1.82-1.75 (m, 1H), 1.49-1.42 (m, 2H), 1.33-1.26 (m, 6H), 0.91-0.87 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$)δ 172.2, 82.3, 78.4, 77.2, 60.9, 40.3, 38.8, 35.2, 28.1, 22.7, 14.1, 14.0 ppm. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{12}H_{22}O_4Na$ 253.1410; Found 253.1411

Ethyl 2-((2S,3S,5R)-5-hexyl-3-hydroxytetrahydrofuran-2-yl)acetate (10): 10 was prepared using same procedure as described for **9**. (0.14 g, yield 85%). $[\alpha]_D^{25}$: -8.4 (*c* 1.0, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max}3463, 2931, 1764. ^1H NMR (700 MHz, $CDCl_3$) δ 4.13-4.05 (m, 3H), 3.98-3.93 (m, 1H), 3.93-3.88 (m, 1H), 2.66 (dd, *J* = 5.3, 16.3 Hz, 1H), 2.45-2.41 (m, 1H), 2.30 (td, *J* = 6.7, 13.0 Hz, 1H), 1.58 (dd, *J* = 4.9, 7.9 Hz, 1H), 1.44-1.41 (m, 2H), 1.30-1.18 (m, 7H), 0.82-0.78 (m, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.4, 79.8, 77.7, 76.8, 60.9, 40.2, 38.6, 35.8, 28.0, 25.7, 22.6, 14.0 ppm. HRMS (ESI) m/z:[M + Na]+ Calcd for $C_{12}H_{22}O_4Na$ 253.1410; Found 253.1411

(3a*S*,5*R*,6a*S*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (1):General procedure for Lactonization reaction: The solution of crude **9** (0.1 g, 0.368 mmol) was treated with catalytic amount of dil. HCl (pH~3) in dry toluene. The reaction mixture was refluxed for 12 h and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using Pet ether: ethyl acetate: (85:15) afforded **1** as a syrupy liquid (0.047 g, 61%). Further chromatography with Pet ether:ethylacetate: (85:15) gave the other isomer **2** as a syrupy liquid (0.009 g, 12.2%). $[\alpha]_D^{25}$: -53.39 (*c* 0.8, $CHCl_3$) [lit.[2b] [α]D = -53.9], ^1H NMR (400 MHz, $CDCl_3$) δ 5.03-5.00 (m, 1H), 4.53-4.50 (m, 1H), 3.97 - 3.91 (m, 1H), 2.73 (d, *J* = 3.3 Hz, 2H), 2.46 - 2.39 (m, 1H), 1.91-1.86 (m, 1H), 1.70-1.65 (m, 1H), 1.60-1.54 (m, 1H), 1.37-1.30 (m, 4H), 0.92-0.89 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$)δ 175.5, 84.7, 80.3, 78.2, 38.3, 36.6, 35.2, 28.2, 22.6, 13.9 ppm. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{10}H_{16}O_3Na$ 207.0991; Found 207.0992

(3a*R*,5*R*,6a*R*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (2):[α] $_D^{25}$: +47.22 (*c* 0.3, $CHCl_3$) [lit.[4] [α]D = +50.9 (*c* = 1.0, $CHCl_3$], ^1H NMR (700 MHz, $CDCl_3$) δ 5.12 (t, *J* = 4.7 Hz, 1H), 4.83-4.79 (m, 1H), 4.07 (dt, *J* = 6.0, 10.7 Hz, 1H), 2.76 (dd, *J* = 6.7, 18.7 Hz, 1H), 2.65 (d, *J* = 18.9 Hz, 1H), 2.38 (dd, *J* = 4.5, 13.9 Hz, 1H), 1.69-1.65 (m, 1H), 1.56-1.43 (m, 2H), 1.39-1.28 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (176MHz, $CDCl_3$) δ 176.0, 84.9, 78.3, 77.3, 38.8, 36.6, 34.4, 28.2, 22.6, 13.9ppm. HRMS (ESI) m/z:[M + Na]+ Calcd for $C_{10}H_{16}O_3Na$ 207.0991; Found 207.0991

(3a*S*,5*R*,6a*S*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (3):(0.046 g, 60%).$[\alpha]_D^{25}$: -39.62 (*c* 0.8, $CHCl_3$) [lit.[2b] [α]D = -41.0],^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (ddd, *J* = 2.3, 4.6, 6.9 Hz, 1 H), 4.53-4.49 (m, 1H), 3.94 (td, *J* = 7.0, 13.8 Hz, 1H), 2.42 (td, *J* = 7.2, 14.2 Hz, 2H), 1.89 (ddd, *J* = 2.3, 7.9, 14.2 Hz, 2H), 1.60-1.50 (m, 4H), 1.37-1.30 (m, 6H), 0.90 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 84.7, 80.4, 78.2, 38.3, 36.4, 35.2, 29.7, 29.6, 28.2, 22.6, 14.0 ppm.HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{12}H_{20}O_3Na$ 235.1302; Found 235.1302

(3a*R*,5*R*,6a*R*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (4): (0.009 g, 12%). $[\alpha]_D^{25}$: +42.78 (*c* 0.5, $CHCl_3$) [lit.[6] [α]D = +50.6 (c 1.0, $CHCl_3$)], ^1H NMR (500MHz, $CDCl_3$) δ 5.13 (t, *J* = 4.7 Hz, 1 H), 4.83 (t, *J* = 5.5 Hz, 1 H), 4.08 (dt, *J* = 6.1, 10.8 Hz, 1 H), 2.77 (dd, *J* = 6.6, 18.8 Hz, 1 H), 2.66 (d, *J* = 18.9 Hz, 1 H), 2.39 (dd, *J* = 4.6, 13.7 Hz, 2 H), 1.73-1.58 (m, 4 H), 1.54-1.43 (m, 2 H), 1.38-1.32 (m, 4 H), 0.93-0.91 (m, 3 H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 84.7, 78.2, 77.3, 38.2, 36.3, 35.2, 31.9, 29.6, 29.3, 22.5, 13.9 ppm. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{12}H_{20}O_3Na$ 235.1304; Found 235.1305

Notes and refernces

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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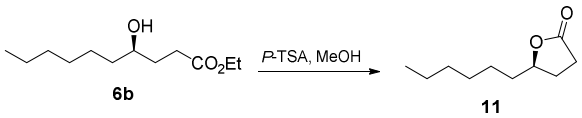
12. Diastereomeric and enantiomeric excess were determined using HPLC (See supporting information).
In order to determine the chiral purity of (*R*)-ethyl-4-hydroxydecanoate **6b**, it was converted into lactone **11** on treatment with *p*-TSA in methanol.



6b **11**

13. The ratio of the mixture was determined by ^{1}H-NMR of crude mixture(See supporting information).
14. The protons H1 H2 H3 H4 and H5 were arbitrarily assigned to show the relative *syn* and *anti*-stereochemistry.

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