Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2985–2988

TETRAHEDRON: *ASYMMETRY*

An efficient and simple synthesis of (−)-wine lactone

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Received 16 October 2001; accepted 7 November 2001

Abstract—A, short and efficient diastereoselective synthesis of (−)-wine lactone (−)-**4a** involving $FeCl_3$/NaI-mediated iodolactonization of γ,δ-unsaturated acid **7** as the key step is described.

1. Introduction

Iodolactonization and iodoetherification are important both as synthetic reactions and for the structural elucidation of organic compounds.[1] Iodolactonization was utilized effectively for stereoselective functional group incorporation and manipulation in Corey's prostaglandin synthesis[1c] as well as in a total synthesis of the tumor inhibitors Vernolepin, and Vernomenin[2] and in vitamin D_2 and D_3 synthesis.[3] Iodolactonization and iodoetherification reactions are important for structural elucidation e.g. from *endo*/*exo* isomeric mixtures, the *endo* isomer gives a quantitative yield of iodolactones and iodoethers, whereas the *exo*-isomer is inert, thus enabling the determination of the proportions of the isomers in the mixture. Because of the importance of the reaction we have recently developed an efficient reagent system viz. $FeCl_3$/NaI for iodolactonization and iodoetherification[4] (Scheme 1).

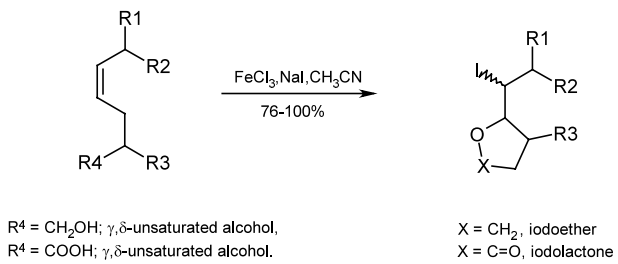
Delighted with the results obtained during the iodolactonization reaction of γ,δ-unsaturated acids mediated by $FeCl_3$/NaI, we extended this methodology to a short and efficient synthesis of the (3a,4,5,7a-tetrahydro 3,6-dimethylbenzofuran-2(3*H*)-ones[5,6] (−)-wine lactone, (−)-**4a** and its *endo*-C(3) epimer (+)-**4b**, which are known odorants of different white wine varieties Recently, (−)-**4a** was also isolated from orange juice and black pepper.[8]

Wine lactone has been synthesized in both racemic[9] and diastereomerically pure form.[7,10] Earlier syntheses are non-stereoselective and lead to the formation of other stereoisomers whereas the recent asymmetric synthesis by Helmchen et al.[10] involves the use of expensive palladium complexes and a large number of steps.

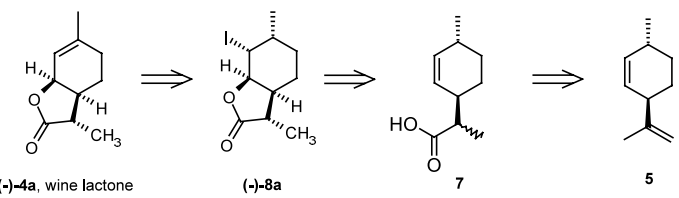
2. Results and discussion

We report herein the diastereoselective synthesis of enantiomerically pure wine lactone (−)-**4a** and its C(3)-epimer (+)-**4b** from (+)-isolimonene **5** employing the iodolactonization protocol developed by us ($FeCl_3$/NaI) as the key step.

The retrosynthetic plan for our synthesis is outlined in Scheme 2.



Scheme 1.



Scheme 2.

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PII: S0957-4166(01)00511-0

As detailed in Scheme 2, the key intermediate iodolactone (−)-**8a** could be obtained by iodolactonization of the corresponding acid **7**. To obtain the γ,δ-unsaturated acid, the ideal starting material was (+)-isolimonene **5** which is a readily available natural product.

To accomplish the synthesis of iodolactones (−)-**8a** and (+)-**8b**, (+)-isolimonene **5** was hydroborated regioselectively with 9-BBN followed by oxidation with alkaline H_2O_2 to furnish alcohol **6** as mixture of diastereomers (d.r. 1:1) in 76% yield (Scheme 3). The diastereomeric mixture of alcohol **6** was oxidized with Jones' reagent to yield the corresponding acid **7** in 78% yield. The diastereomeric mixture of γ,δ-unsaturated acid **7** was then subjected to the iodolactonization protocol developed by us[4] using the $FeCl_3$/NaI reagent system (for 1 equiv. of the acid, 2 equiv. each of $FeCl_3$ and NaI were used in refluxing CH_3CN). This furnished the diastereomeric iodolactones (−)-**8a** and (+)-**8b** in 59% overall yield in the ratio 60:40. It is pertinent to mention that the conventional iodolactonization protocol (I_2, saturated $NaHCO_3$)[1d,e,f] furnished the iodolactones in somewhat lower yield (52%). At this stage the diastereomers (−)-**8a** and (+)-**8b** were separated by careful column chromatography (60–120 silica gel, eluent: ethyl acetate:pet. ether 0.75:99.25).

Dehydrohalogenation of iodolactone (−)-**8a** with DBU in THF furnished natural (−)-wine lactone (−)-**4a** in 76% yield. The wine lactone thus obtained had identical spectral properties (^1H and ^{13}C NMR, IR) and specific rotation as compared to a sample of the natural isomer. Additionally the synthetic wine lactone was found to have >99% e.e. as judged by GC analysis on Chrompack β-CD (25 m×0.25 mm) at 180°C. Similarly, the diastereomeric iodolactone (+)-**8b** was also dehydrohalogenated with DBU to furnish the C(3)-epimer (+)-**4b**. Alternatively, wine lactone (−)-**4a** could be readily converted[10] to its C(3)-epimer (+)-**4b**.

3. Experimental

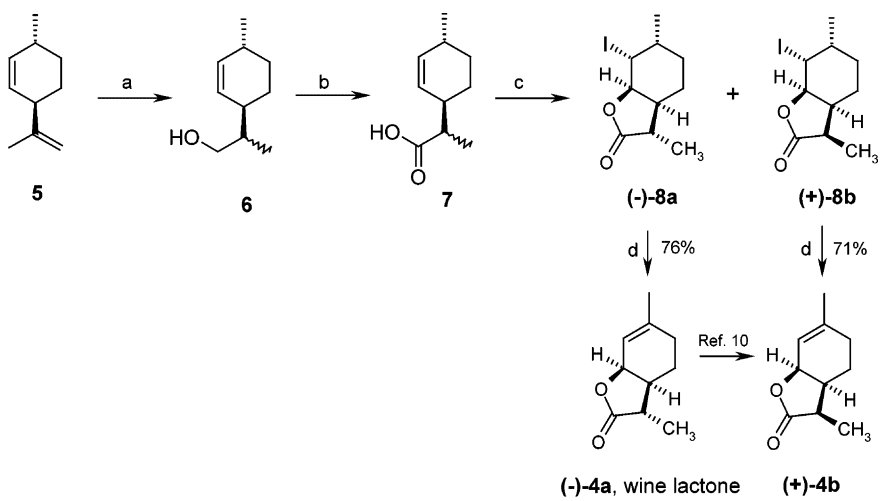
3.1. General comments

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on 200 and 50 MHz in $CDCl_3$ using TMS as an internal standard. IR spectra were recorded in $CHCl_3$ on FT-IR spectrometer. GC analysis was performed on Chrompack β-CD (25 m×0.25 mm) at 180°C. Optical rotations were recorded on a Jasco P-1020 polarimeter using sodium vapor lamp. THF was freshly distilled from sodium benzophenone ketyl prior to use. Starting material (+)-isolimonene **5** was purified by column chromatography prior to use. The alcohol **6**[11] and acid **7**[12] were prepared by literature methods. All the reactions were monitored by TLC on 0.25 mm Merck Kieselgel TLC plate using ethanolic *p*-anisaldehyde solution with heating for visualization. Chromatography was performed on silica gel (60–120 mesh).

3.2. Idolactones (−)-8a and (+)-8b

To a solution of acid **24** (1.5 g, 8.93 mmol) in acetonitrile (12 mL) was added anhydrous $FeCl_3$ (2.901 g, 17.86 mmol) and NaI (2.68 g, 17.86 mmol), in CH_3CN (35 mL). The solution was stirred under reflux for 2.5 h. The reaction mixture was then cooled to room temperature, quenched with water (8 mL) and extracted with dichloromethane (4×30 mL). The organic layer was washed with saturated $Na_2S_2O_3$ (25 mL), water (25 mL), and finally with brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator under reduced pressure to furnish the crude mixture of epimeric iodolactones (−)-**8a** and (+)-**8b** in the ratio 60:40 (1.55 g, 59%). The iodolactones were separated by careful column chromatography (60–120 mesh, eluent: ethyl acetate:pet ether 0.75:99.25)

Iodolactones (−)-**8a** and (+)-**8b** were also obtained as an epimeric mixture by the conventional method using



Scheme 3. (a) (i) 9-BBN, THF, 0°C–rt, 15 h, (ii) NaOH, H_2O_2, 0°C–rt, 1 h, 76%; (b) Jones' oxidation, 0°C–rt, 2 h, 78%; (c) NaI/$FeCl_3$, CH_3CN, reflux, 2.5 h, 59%; (d) DBU/THF, rt, 5 h.

saturated $NaHCO_3/I_2$ in diethyl ether at 0°C in 52% yield.[1f]

3.2.1. [(3*S*,3a*S*,6*R*,7*R*,7a*R*)-(3a,4,5,6,7,7a)-Hexahydro-3,6-dimethylbenzofuran-2(3*H*)-one, iodolactone (−)-8a. Mp 75–76°C; e.e. = 98.99%; t_R [(−)-**8a**]: 29.152 min; $[\alpha]_D^{20}$ −37.3 ($c = 3$, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 2965, 2873, 1780, 1455, 1385; ^1H NMR (200 MHz, $CDCl_3$): δ 1.01 (d, 3H, $J = 6.34$ Hz, -CHCH_3), 1.29 (d, 3H, $J = 7.33$ Hz, -COCHCH_3), 1.39–1.47 (m, 4H, -CH_2), 1.81–1.93 (m, 1H, -COCHCH$_3$), 2.35–2.51 (m, 2H, -CH_2), 4.66 (t, 1H, $J = 3.76$ Hz, -CHI), 4.92 (dd, 1H, $J = 3.92$ Hz, -CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.02 (q, -CHCH$_3$), 22.26 (q, -COCHCH$_3$), 26.37 (t, -CH$_2$), 28.06 (t, -CH$_2$), 31.81 (d, -CHCH$_3$), 38.81 (d, -CH), 41.55 (d, -CHI), 43.39 (d, -COCHCH$_3$), 81.73 (d, CHO), 179.07 (s, CO). Mass (m/z): 294 (M^+, 8), 167 (76), 149 (18), 121 (48), 93 (100), 81 (32), 67 (11), $C_{10}H_{15}IO_2$ (294.13). Calcd: C, 40.83; H, 5.14; I, 43.14; found: C, 40.90; H, 5.20; I, 42.71%.

3.2.2. [(3*R*,3a*S*,6*R*,7*R*,7a*R*)-(3a,4,5,6,7,7a)-Hexahydro-3,6-dimethylbenzofuran-2(3*H*)-one, iodolactone (+)-8b. Mp 72–73°C; e.e. = 99.06%; t_R [(+)-**8b**]: 31.022 min, $[\alpha]_D^{20}$ +21.63 ($c = 3$, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 2965, 2934, 2875, 1781, 1455, 1385, 1328; ^1H NMR (200 MHz, $CDCl_3$): δ 0.94 (d, 3H, $J = 5.37$ Hz, -CHCH_3), 1.29 (d, 3H, $J = 6.98$ Hz, -COCHCH_3), 1.21–1.43 (m, 4H, -CH_2), 1.64–1.75 (m, 1H), 2.74–2.83 (m, 2H), 4.72–4.77 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.93 (q, -CHCH$_3$), 23.28 (t, CH$_2$), 23.70 (q, -COCHCH$_3$), 27.85 (t, -CH$_2$), 30.66 (d, -CHCH$_3$), 35.66 (d, -CH), 42.25 (d, -CHI), 42.59 (d, -COCHCH$_3$), 82.23 (d, CHO), 179.07 (s, CO). Mass (m/z): 294 (M^+, 7), 167 (94), 149 (18), 121 (54), 93 (100), 77 (12), 67 (8), $C_{10}H_{15}IO_2$ (294.13). Calcd: C, 40.83; H, 5.14; I, 43.14; found: C, 40.95; H, 5.02; I, 42.83%.

3.2.3. (−)-(3*S*,3a*S*,7a*R*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one: wine lactone, (−)-4a. A solution of (−)-**8a** (0.250 g, 0.85 mmol) and DBU (0.166 g, 1.09 mmol) in dry tetrahydrofuran (10 mL) was stirred at room temperature for 5 h. Aqueous HCl (6N, 15 mL) was added and the mixture was extracted with diethyl ether (4×20 mL). The combined organic layer was washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4, concentrated on rotary evaporator at reduced pressure to furnish crude wine lactone (−)-**4a**. The lactone was purified by column chromatography (eluent: ethyl acetate:pet. ether 1:99). The lactone was further purified by crystallization from ethyl acetate/hexane. Yield: 0.107 g (76%); mp (Lit.): 49–50°C (48–50°C); e.e. = 99.58%; t_R [(−)-**4a**]: 10.939 min, $[\alpha]_D^{20}$ (Lit.): −13.5 ($c = 3$, $CHCl_3$), [−13.1 ($c = 3$, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1}: 3020, 2981, 2935, 1761, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (d, 3H, $J = 7.39$ Hz, CHCH_3), 1.73 (s, 3H, HC=CCH_3), 1.77–2.02 (m, 4H, CH_2), 2.19–2.32 (m, 1H, -CH-CH-CH$_3$), 2.34–2.45 (m, 1H, -CHCH$_3$), 4.85–4.90 (m, 1H, CHO), 5.51 (m, 1H, C=CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.62 (q, CHCH$_3$), 21.85 (t, CH$_2$), 23.29 (q, C=CH$_3$), 25.53 (t, CH$_2$), 37.11 (d, CHCH$_3$), 39.90 (d, CHCHCH$_3$), 74.89 (d, CHO), 18.49 (d, =CH), 140.84 (s, CH$_3C$=), 179.51 (s, C=O). Mass (m/z): 166 (M^+, 22), 151 (37), 138 (12), 123 (14), 107 (40), 93 (100), 79 (87), 67 (52), 55 (88). $C_{10}H_{14}O_2$ (166.22). Calcd: C, 72.26; H, 8.49; found: C, 72.37; H, 8.46%.

3.2.4. (+)-(3*R*,3a*S*,7a*R*)-3a,4,5,7a-Tetrahydro-3,6-dimethylbenzofuran-2(3*H*)-one: (+)-4b. A solution of (+)-**8b** (0.250 g, 0.85 mmol) and DBU (0.166 g, 1.09 mmol) in dry tetrahydrofuran (10 mL) was stirred at room temperature for 5 h. Aqueous HCl (6N, 15 mL) was added and the mixture was extracted with diethyl ether (4×20 mL). The combined organic layer was washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4, concentrated on rotary evaporator at reduced pressure to furnish crude wine lactone (+)-**4b**. The lactone was purified by column chromatography (eluent: ethyl acetate:pet. ether 1:99). The lactone was further purified by crystallization from ethyl acetate/hexane. Yield: 0.1 g (71%); mp (Lit.): 58–60°C (57–59°C); e.e. = 99.86%; t_R [(−)-**4a**]: 13.271 min, $[\alpha]_D^{20}$ (Lit.) +112.15; ($c = 3$, $CHCl_3$), [+112, ($c = 3$, $CHCl_3$)] IR ν_{max} ($CHCl_3$) cm^{-1}: 3020, 2981, 2935, 1761, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ 1.12–1.16 (m, 1H, CH_2), 1.19 (d, 3H, $J = 7.35$ Hz, CHCH_3), 1.66–1.70 (m, 1H, CH_2), 1.79 (s, 3H, CH=CCH_3), 1.95–2.03 (m, 2H, CH_2), 2.23–2.31 (m, 1H, CHCHCH$_3$), 2.89 (dq, 1H, $J = 7.52$ Hz, $J = 7.33$ Hz, CH-CH$_3$), 4.60–4.64 (m, 1H, CHO), 5.65–5.68 (m, 1H, HC=C); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.13 (q, CHCH$_3$), 19.51 (t, CH$_2$), 23.62 (q, C=CH$_3$), 28.73 (t, CH$_2$), 37.62 (d, CHCHCH$_3$), 40.05 (d, CHCH$_3$), 74.56 (d, CHO), 116.80 (s, =CH), 143.92 (s, H$_3$CC=), 178.33 (s, C=O). Mass (m/z): 166 (M^+, 32), 151 (57), 138 (12), 123 (19), 93 (100), 79 (65), 55 (39); $C_{10}H_{14}O_2$ (166.22). Calcd: C, 72.26; H, 8.49; found: C, 72.40; H, 8.52%.

4. Conclusions

Thus, we have achieved a short and efficient synthesis of (−)-wine lactone from (+)-isolimonene utilizing the iodolactonization protocol developed by us ($FeCl_3$/NaI) as the key step.

Acknowledgements

R.K.K., A.K.S. and S.P.C. thank CSIR, New Delhi for senior research fellowships. Funding from Young Scientist Award, CSIR, New Delhi is also gratefully acknowledged.

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