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A new chiral route to 5- and 6-substituted hydropyran-2-ones utilizing enantiopure 4-cumyloxy-2-cyclopenten-1-one

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Abstract—Starting from enantiopure 4-cumyloxy-2-cyclopenten-1-one, a route to 5- and 6-substituted hyropyran-2-ones has been developed. The method has achieved the synthesis of 4,5-*cis*- and 4,5-*trans*-5-ethyl-4-hydroxytetrahydropyran-2-ones assigned to marine natural products simplactones A and B to disprove the former and revise the latter of the proposed structures.

Although a number of synthetic procedures for the construction of 6-substituted hydropyran-2-one derivatives have been reported so far, there is no efficient general route to 5-substituted hydropyran-2-one derivatives.[1] We report here a new route to 5- and 6-substituted hydropyran-3-ones **1**–**4** utilizing enantiopure 4-cumyloxy-2-cyclopenten-1-one **5** whose efficient synthesis in both enantiomeric forms has been established recently[2] (Fig. 1). We explored a route to 5-substituted hydropyran-2-one derivatives from **5** targeting a naturally occurring 5-substituted hydropyran-2-ones, (–)-simplactone A[3] **1** and (–)-simplactone B[3] **2**, along with structurally defined compounds, **3a**,[4] **b**[5] and **4a**,[6] **b**,[5] having a 6-substituted hydropyran-2-one structure on the basis of the same methodology to confirm the absolute configuration of the target natural products. Simplactones A **1** and B **2** were isolated from the Caribbean sponge; *Plakortis simplex*; their structures were proposed based on spectroscopic analyses and assigned as 4*R*,5*S*-5-ethyl-4-hydroxytetrahydropyran-2-one for the former and as 4*R*,5*R*-5-ethyl-4-hydroxytetrahydropyran-2-one for the latter.[3]

The basis of the present study utilizing **5** is a diastereoselective 1,4-addition placing an incoming nucleophile opposite the cumyloxy functionality. If an

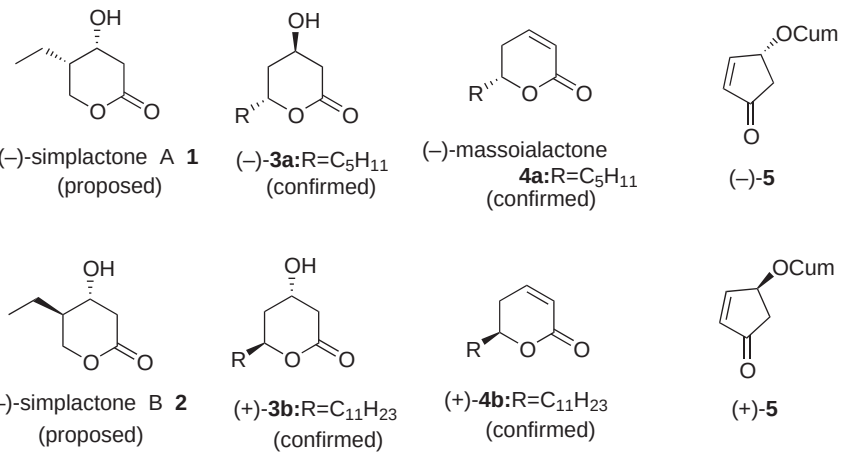

Figure 1.

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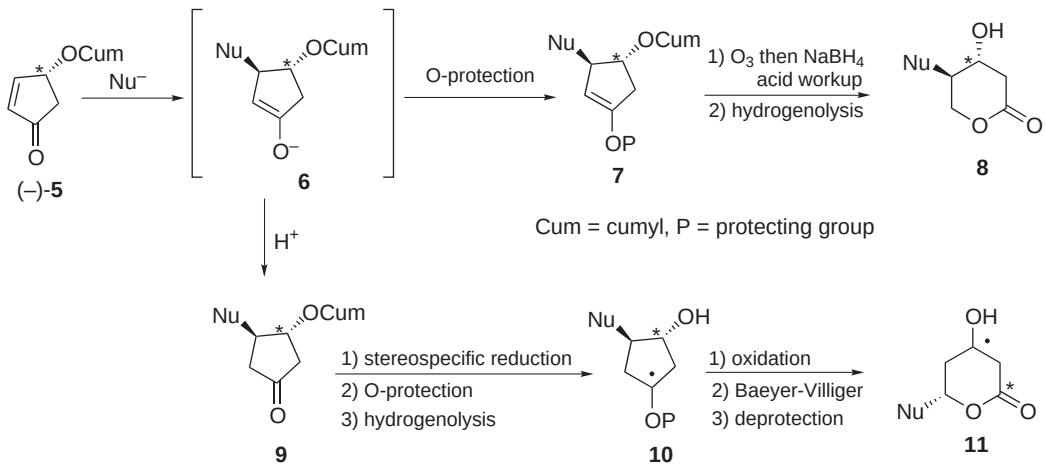
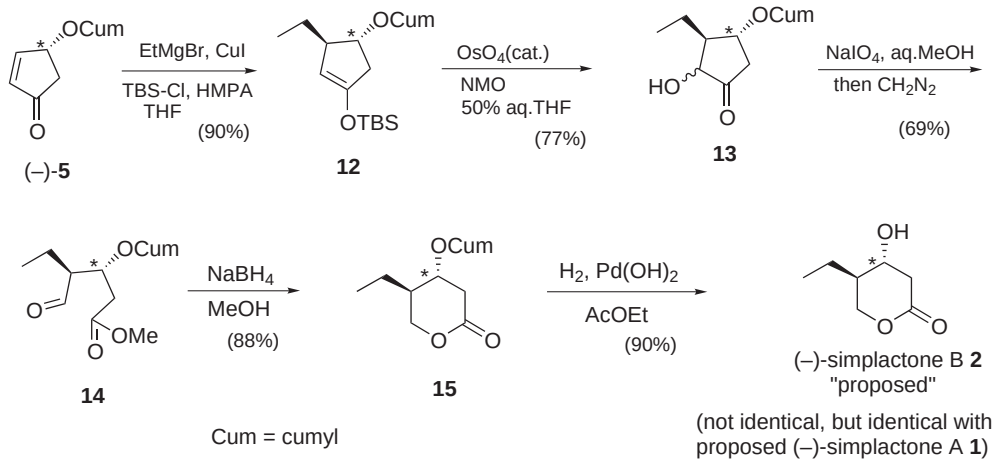
enolate intermediate **6** could be trapped as an enol ether **7**, it would afford a 5-substituted 3-hydroxy tetrahydropyran-2-one **8** on sequential oxidative cleavage of the enol double bond, chemoselective reduction of the formyl carbonyl and removal of the cumyl functionality. On the other hand, if an enolate **6** could be isolated as a ketone **9**, it could be transformed into a cyclopentanol **10** on sequential stereospecific reduction, *O*-protection, and decumylation. On further sequential oxidation, Baeyer–Villiger reaction, and deprotection, **10** could furnish a 6-substituted 3-hydroxytetrahydropyran-2-one **11** isomeric to **8** (Scheme 1).

To realize the enol ether route, we first examined the synthesis of (–)-simplactone B **2** having 4*R*,5*R*-4,5-*trans*-stereochemistry as its stereocontrol seemed much easier than the *cis*-counterpart simplactone A **1**. Thus, (–)-**5**, $[\alpha]_D^{25}$ −62.7 (*c* 3.9, $CHCl_3$) (>99% ee), was treated with a cuprate generated from ethylmagnesium bromide in THF containing HMPA followed by *tert*-butyldimethylsilyl chloride (TBS-Cl) in the same flask[7] to give the TBS-enol ether **12**, $[\alpha]_D^{26}$ −88.3 (*c* 1.3, $CHCl_3$), in good yield. The TBS-ether **12** obtained was then dihydroxylated with a catalytic amount of Os(IV) oxide and 4-methylmorphorine *N*-oxide (NMO) in aqueous THF to give the acyloin **13** as an epimeric mixture. Ketone transposition affording the isomeric acyloin did not take place under these conditions. Periodate cleavage of **13** yielded the γ-formyl ester **14**, $[\alpha]_D^{29}$ +75.3 (*c* 1.3, $CHCl_3$), after workup with diazomethane, which was then reduced with sodium borohydride to give the 4,5-disubstituted tetrahydropyran-2-one **15**, mp 49–50°C, $[\alpha]_D^{29}$ −37.8 (*c* 1.1, $CHCl_3$), by concurrent lactonization. Finally, the cumyl functionality was removed by hydrogenolysis to afford (–)-simplactone B **2**. However, the product, obtained in 38% overall yield from the starting (–)-**5**, was found to be different from our target; its spectroscopic data (IR, ^1H and ^{13}C NMR) were not identical with those reported for (–)-simplactone B **2**, but with those of (–)-simplactone A **1** assigned to have 4,5-*cis*-configuration though the synthetic material had much higher optical rotation value, $[\alpha]_D^{28}$ −23.9 (*c* 0.8, $CHCl_3$) {lit.:[3] $[\alpha]_D^{25}$ −3 (*c* 0.002, $CHCl_3$)}. Thus, this concluded that the originally assigned 4′*R*,5′*S*-4,5-*cis*-structure for (–)-simplactone B **2′** should be corrected as 4′*R*,5′*R*-4,5-*trans*-structure originally assigned for (–)-simplactone ′ A **1′** (Scheme 2).



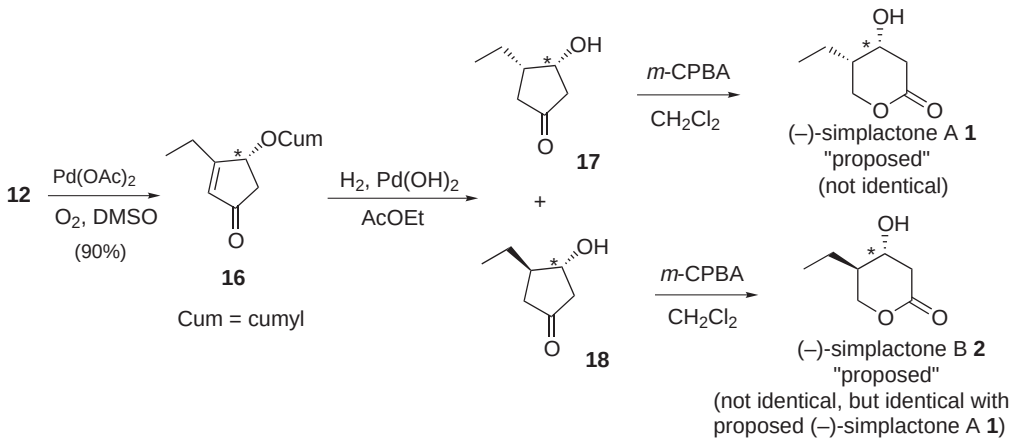
Scheme 1.



Scheme 2.

To obtain the 'proposed' (−)-simplactone A **1** having 4*R*,5*S*-4,5-*cis*-configuration, the above TBS-ether **12** was treated under Saegusa[8]–Larock[9] conditions using a catalytic amount of palladium(II) acetate (10 mol%) in DMSO under an oxygen atmosphere to give cyclopentenone **16** in 90% yield. Although diastereocontrolled hydrogenation could not be attained, **16** furnished a separable 1:1 mixture of keto-alcohols, *cis*-**17** and *trans*-**18**, with concomitant removal of the cumyl functionality on catalytic hydrogenation. As hydroxy-directed regioselective Baeyer–Villiger oxidation of a 3-hydroxycyclopentanone was reported,[10] we treated these two with *m*-chloroperbenzoic acid in dichloromethane. Though the reaction proceeded very slowly, **17** furnished an inseparable 4.5:1 mixture containing 'proposed' simplactone A **1** as the major component and its regio-isomer as the minor component. On the other hand, the *trans*-**18** furnished the *trans*-lactone identical with 'proposed' simplactone B **2** as the sole product. The major component of the mixture obtained from **17** showed virtually the same ^{1}H NMR spectrum, but its ^{13}C NMR spectrum was significantly different from the reported one for 'proposed' simplactone A **1**. Thus, we cannot help concluding the proposed structure of (−)-simplactone **1** should be corrected though the proper structure could not be determined (Scheme 3, Table 1).

Since there are some precedents[11] exhibiting *syn*-selective 1,4-addition in the related cyclopentenone derivatives, we explored the synthesis of structure-defined compounds having a 4,6-disubstituted tetrahydropyran-1-one structure to ascertain the *anti*-selective 1,4-addition of our cyclopentenone **5** by employing the ketone route. Targeting the naturally occurring **3a** and the key intermediate **3b** of (−)-tetrahydrolipstatin **23**, (−)-**5** was reacted with a cuprate prepared in situ from pentylmagnesium bromide in the presence of TMS-Cl in ether containing HMPA to furnish diastereoselectively the ketone **19a**, $[\alpha]_D^{29}$ −65.8 (*c* 0.9, $CHCl_3$), as a single



Scheme 3.

Table 1. ^{1}H and ^{13}C NMR spectra of natural[a] and synthetic[b] simplactones A and B

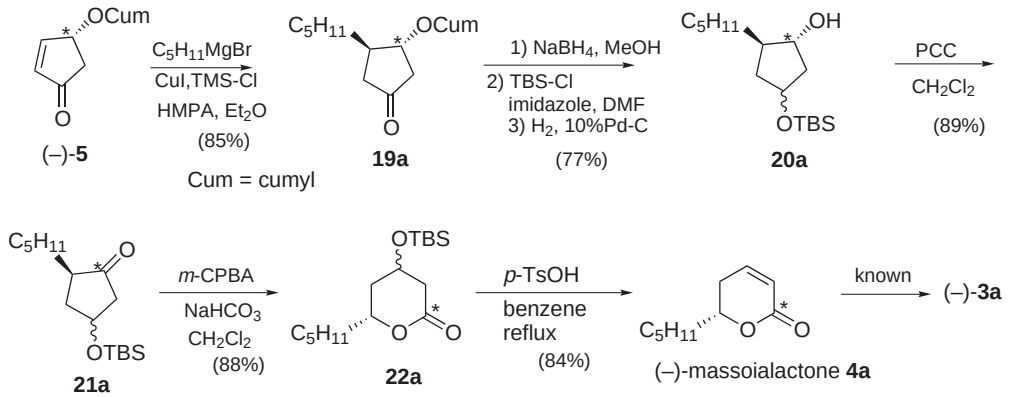
	Simplactone **A** Natural		Simplactone **B** Synthetic		Simplactone **B** Natural		Simplactone **A** Synthetic	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	170.2		171.6		170.3		170.1	
5	69.0	4.49 (1H, dd, J=11.4, 4.4 Hz) 3.98 (1H, overlapped)	69.3	4.49 (1H, dd, J=11.5, 4.6 Hz)	68.5	4.36 (1H, dd, J=11.2, 10.5 Hz) 4.25 (1H, dd, J=11.2, 4.6 Hz)	68.9	4.36 (1H, dd, J=10.8, 10.8 Hz) 4.25 (1H, dd, J=11.3, 4.5 Hz)
3	68.1	3.97 (1H, overlapped)	67.7	3.98 (2H, dd, J=11.5, 8.0 Hz)	67.1	4.21 (1H, t, J=10.1 Hz)	64.6	4.21 (1H, br s)
2	42.4	2.88 (1H, dd, J=17.5, 5.8 Hz) 2.55 (1H, dd, J=17.5, 5.5 Hz)	42.3	2.86 (1H, dd, J=17.6, 5.8 Hz) 2.55 (1H, dd, J=17.6, 5.8 Hz)	42.4	2.72 (1H, overlapped) 2.71 (1H, overlapped)	39.4	2.71 (2H, t, J=4.1 Hz)
4	38.2	1.78 (1H, m)	38.0	1.79 (1H, m)	37.5	1.87 (1H, m)	39.2	1.87 (1H, m)
6	21.6	1.65 (1H, m)1.36 (1H, m)	21.6	1.64 (1H, m) 1.36 (1H, m)	20.6	1.47 (1H, m) 1.36 (1H, m)	19.6	1.46 (1H, m) 1.36 (1H, m)
7	11.2	1.01 (3H, t, J=7.5 Hz)	11.1	1.01 (3H, t, J=7.6 Hz)	11.8	1.00 (3H, t, J=7.3 Hz)	11.2	1.00 (3H, t, J=7.3 Hz)
OH		1.84 (1H, br d, J=4.1 Hz)		2.60 (1H, br s)		1.68 (1H, br.d, J=2.8 Hz)		2.41 (1H, br s)

[a] NMR spectra were measured in $CDCl_3$ (^{13}C: 125 MHz and ^{1}H: 500 MHz).[3]
[b] NMR spectra were measured in $CDCl_3$ (^{13}C: 75 MHz and ^{1}H: 300 MHz).

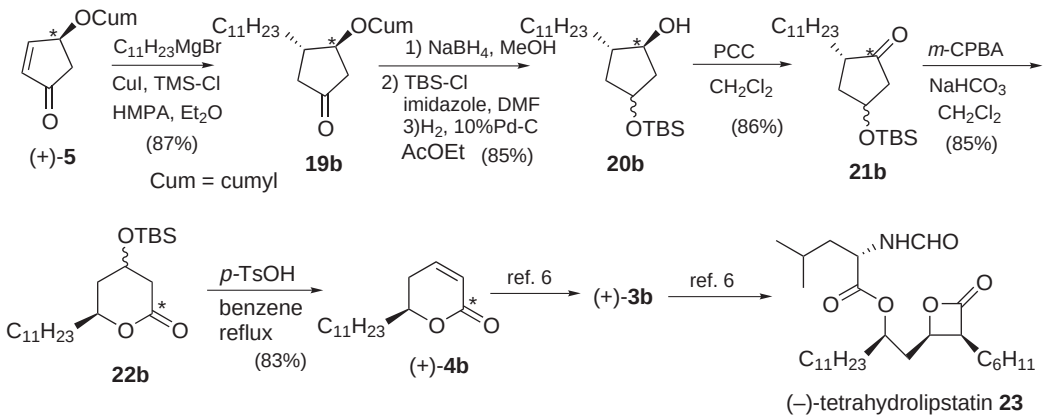
product. Although extensive examination was made, diastereoselective reduction of the ketone **19a** could not be attained, and the reduction product obtained as a mixture of two diastereomers was transformed into a mixture of the *tert*-butyldimethylsilyl (TBS) ether **20a** by sequential silylation and catalytic de-*O*-cumylation. Oxidation of **20a** followed by the Baeyer–Villiger oxidation of the resulting ketone **21a** afforded the 4,6-disubstituted tetrahydropyran-1-one **22a** as an inseparable mixture of two C4-epimers. The mixture was refluxed in benzene with a catalytic amount of *p*-toluenesulfonic acid to give (−)-massoialactone **4a**, $[\alpha]_D^{28}$ −109.7 (*c* 3.9, $CHCl_3$){lit.[12]: $[\alpha]_D^{29}$ −107.52 (*c* 1.07, $CHCl_3$)}, isolated from the bark of *Cryptocrya massoia* and having 6*R* configuration. The product obtained as a single product had the same characteristics as those of an authentic material prepared by a completely different procedure[12] to support the *anti*-1,4-addition pathway as well as to support our product above having 4-hydroxy-5-ethyltetrahydropyran-2-one as *trans*-4,5 with 4*R*,5*R*-configuration proposed to (−)-simplactone B **2** though it possessed the spectroscopic data assigned to (−)-simplactone A **1** having the *cis*-4,5-4*S*,5*R*-structure. Overall yield of (−)-**4a** from (−)-**5** was 43% in seven steps. This synthesis constitutes a formal acquisition of (−)-**4a** as it has been previously prepared diastereoselectively from (−)-**3a**[1b,12,13] (Scheme 4).

The *anti*-1,4 addition pathway was further supported by reaction using the enantiomeric starting material. Thus, the reaction of (+)-**5**, $[\alpha]_D^{26}$ +62.9 (*c* 1.9, $CHCl_3$) (>99% ee), with a cuprate generated from dodecylmagnesium bromide under the same conditions above gave the single (+)-ketone **19b**, $[\alpha]_D^{25}$ +54.8 (*c* 2.4, $CHCl_3$), excellently, which was transformed into 6*S*-dodecyl-5,6-dihydropyran-2- one (+)-**4b**, mp 45–47°C, $[\alpha]_D^{26}$ +74.4 (*c* 1.8, $CHCl_3$) {lit.:[14] $[\alpha]_D^{26}$ +75.38 (*c* 6.54, $CHCl_3$)}, by employing exactly the same procedure above via a diastereomeric mixture of the cyclopentanol **20b**, cyclopentanone **21b**, and δ-lactone **22b**. As (+)-**4b** was obtained by a completely different procedure[5] and was transformed into (+)-tetrahydrolipstatin[5] **23** after diastereocontrolled conversion into 4*S*,6*S*-6-dodecyl-4-hydroxytetrahydropyran-2-one (+)-**3b**, the present synthesis constitutes a formal alternative synthesis of **23**. Overall yield of (+)-**4b** from (+)-enone **5** was 45% in seven steps (Scheme 5).

In conclusion, we have developed a new diastereocontrolled route to both enantiomeric 5- and 6-substituted 4-hydroxytetrahydropyran-2-one derivatives using enantiopure 4-cumyloxy-2-cyclopenten-2-one as the chiral building block. Although direct stereocontrolled introduction of a 3-hydroxy functionality in 6-substituted tetrahydropyran-2-ones could not be accom-



Scheme 4.



Scheme 5.

plished, a convenient route to rather less accessible 4-hydroxy-5-substituted tetrahydropyran-2-one derivatives has been established using the same chiral starting material.

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References

1. (a) Collins, J. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377 and previous report; (b) Takano, S.; Shimazaki, Y.; Moriya, M.; Ogasawara, K. *Chem. Lett.* **1990**, 1177.
2. Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **2000**, 817.
3. Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, *Tetrahedron* **1999**, *55*, 13831.
4. (a) Vesonder, R. F.; Stodola, F. H.; Rohwedder, W. K. *Can. J. Biochem.* **1972**, *50*, 36; (b) Bennett, F.; Knight, D. W. *Heterocycles* **1989**, *29*, 639; (c) Bennett, F.; Knight, D. W.; Fenton, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1543.
5. Mori, K. *Agr. Biol. Chem.* **1976**, *40*, 1617.
6. Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743.
7. (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025; (b) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.
8. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
9. Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Teterahedron Lett.* **1995**, *36*, 2423.
10. Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovukulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714.
11. (a) Yakura, T.; Tanaka, K.; Iwamoto, M.; Nameki, M.; Ikeda, M. *Synlett* **1999**, *33*, 917; (b) Yakura, T.; Tanaka, K.; Kitano, T.; Uenishi, J.; Ikeda, M. *Tetrahedron* **2000**, *56*, 7715.
12. Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 533.
13. Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539.
14. Private communication from Professor Ghosh, Department of Chemistry, University of Illinois at Chicago, USA.