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Crotylation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde: a simple synthesis of (+)-*trans*-oak lactone

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ABSTRACT

Crotylations of (*R*)-2,3-cyclohexylideneglyceraldehyde (**1**) were utilized in a simple synthesis of *trans*-oak lactone (**I**), a representative example of chiral β,γ-disubstituted-γ-butyrolactones. In this endeavor, crotylations of **1** in THF mediated with four low valent metals were studied. All these reactions took place efficiently producing **2** in good yields but with varied stereoselectivities. Each reaction produced the corresponding secondary alcohol adduct **2b** and **2c** predominantly with diastereoisomer **2a** only in trace amounts. Among these four reactions, only Sn-mediated addition yielded **2b** as the major products. Later, **2c** was converted into **2d** through oxidation–reduction. Finally, **2c** was transformed into *trans*-oak lactone **I** in a few steps. Following this route, **2a**, **2b**, and **2d** would produce other stereoisomers of oak lactone.

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1. Introduction

γ-Butyrolactones are the constituents of many biologically active natural products.[1] Their enantiopurity and absolute configuration often affect their physiological activities.[2] Additionally, optically active γ-butyrolactones are useful as chiral synthons for their versatile application in the synthesis of bioactive compounds.[1,3] Chiral β,γ-disubstituted-γ-butyrolactones, due to their varied biological activities, have drawn considerable attention for their synthesis over the ages.[4] Furthermore, the correlation between optical rotations and different conformations of *trans*-β,γ-disubstituted γ-lactones drew attention of organic chemists.[5]

(4*S*,5*R*)-*trans*-(**A**) and (4*S*,5*S*)-*cis*-(**B**) 5-butyl-4-methyl butyrolactones, known as oak lactones (Fig. 1), are extracted as the major compounds from wood in alcoholic beverages during fermentation and/or storage in oak barrels.[6] Their corresponding (4*R*,5*S*)-*trans*-(***ent*-A**) and (4*R*,5*R*)-*cis*-(***ent*-B**) enantiomers are also present in the same beverages. The aroma of alcoholic beverages is believed to be due to the presence of pure diastereomers of these lactones.[6] Compounds **A** and **B** are good examples of chiral *trans*-β,γ- and *cis*-β,γ-disubstituted γ-butyrolactones, respectively. Hence, apart from obtaining them in sufficient amount for their extensive biological screening, any synthesis of them assumes good significance from synthetic viewpoint specially to evaluate the applicability of the approach for stereo-selective construction of other compounds possessing β,γ-disubstituted γ-butyrolactone units. So far, several syntheses of **A** and **B** were reported in the literature.[7] Among them, Brown et al.[7b] synthesized all four stereoisomers of oak lactone. In our ongoing program on the synthesis of bioactive compounds we are making versatile use of easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde (**1**)[8a] to synthesize different molecules possessing varied structural features.[8a–h] We present herein its another simple application to develop a simple route for stereodivergent syntheses of all four stereoisomers of oak lactone. In this Letter, this has been exemplified by the total synthesis of *trans*-oak lactone (**A**).

Retrosynthetic analysis (Scheme 1) of **A** suggested that crotylation of **1** should be a straightforward approach to begin with. This would enable us to introduce two contiguous stereo-centers in **A** including the methyl branching at its C-4 position at an initial stage. There are several well-known procedures for stereo-differentiating crotylations[9] of aldehydes that are performed in highly anhydrous conditions. Schlapbach and Hoffman[7d] synthesized only (4*S*,5*R*)-*trans*-(**A**) through asymmetric crotylboration of an aldehyde. In recent years, there has been considerable attention on per-

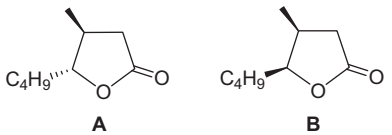

Figure 1. Structures of *trans*-oak lactone (**A**) and *cis*-oak lactone (**B**).

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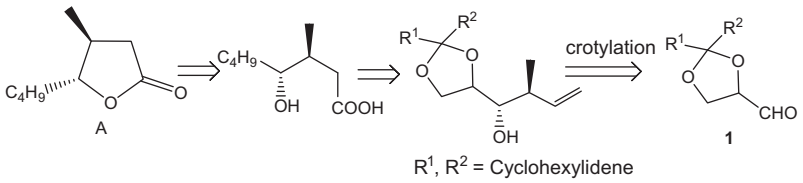


Scheme 1. Retrosynthesis of *trans*-oak lactone (**A**).

forming organic reactions in wet solvents, aqueous medium, or salt solutions[10] with a view to attaining their practical viability. This prompted us to give an effort to crotylate **1** in moist reaction conditions mediated with several low valent metals.[11] This also gave us an opportunity to compare the efficacy and stereo-selectivity (Table 1) of all these low valent metal-mediated reactions with those observed by us earlier[8b] for the same reaction using Luche's procedure.[12] First, **1** was crotylated (Scheme 2) following mediation with either of low valent Cu, Co, and Fe that were prepared in situ by reduction of their salts with Zn[11a] (Table 1, entries a–c). Also, the same reaction was performed (Scheme 2) following mediation with low valent Sn, which was prepared in situ by reduction of commercially available $SnCl_2$, $2H_2O$ [$E^0_{Sn=Sn^{2+}+2e} = +0.136$ V] with zinc [$E^0_{Zn=Zn^{2+}+2e} = +0.761$ V] (Table 1, entry d). All the four reactions were carried out[13] using excess amount of commercially available crotyl bromide (Fluka make, mixture of cis and trans, 1:5), the metal salt and reducing metal (zinc) to ensure their smooth progress. The results of all crotylation reactions are given below in Table 1.

2. Results

In all these four cases, reactions progressed smoothly and with absolute regioselectivity giving only the γ-addition product **2** in good yields (Table 1). Among the four, the yield of Fe-mediated reaction was found to be the best (Table 1, entry b) and was even better than that obtained earlier[8b] following Luche's procedure. It is worthy to note that Fe- and Sn-mediated crotylation of **1** took place at much faster rates (Table 1, entries b and d) than the other two (Table 1, entries a and c) and also the earlier one.[8b] Thus, employing bimetallic redox strategy[11] all the four low valent metals (Cu, Fe, Co, and Sn) were found to be good mediators with varied efficacies to crotylate aldehyde **1** and again in wet solvent.

Table 1
Crotylation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**1**)

Entry	Reagents	Time	Products	Yield[a] (%)	Products Ratio
a	$CoCl_2$, $6H_2O$; Zn	24 h	**2a**, **2b**, **2c**	78	**2a**:**2b**:**2c**:: 3.8:47.5:48.7
b	$FeCl_3$/Zn	10 min	**2a**, **2b**, **2c**	87	**2a**:**2b**:**2c**:: 1.5:48.4: 50.1
c	$CuCl_2$, $2H_2O$; Zn	15 h	**2a**, **2b**, **2c**	79	**2a**:**2b**:**2c**:: 4.2:29.5:66.3
d	$SnCl_2$, $2H_2O$; Zn	45 min	**2a**, **2b**, **2c**	80	**2a**:**2b**:**2c**:: 7.1:78.2:14.7

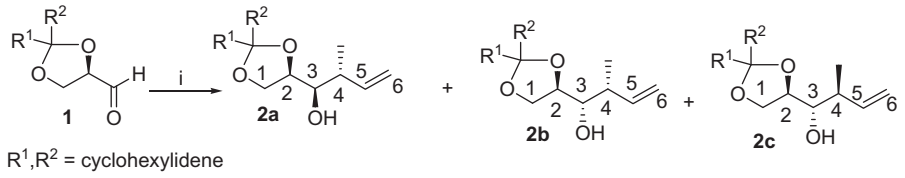
[a] The nearest rounded figures of all yields were given here.

3. Stereochemistry

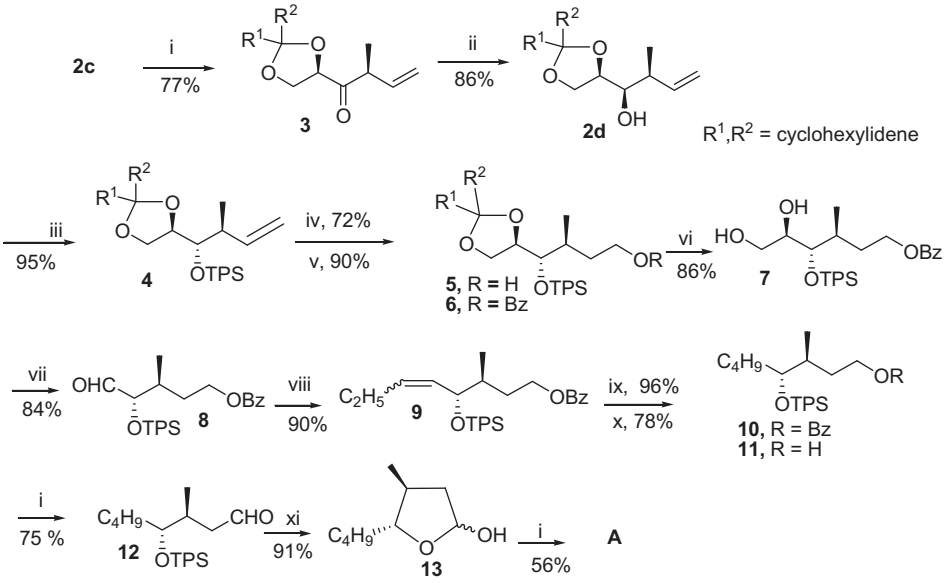
Interestingly, all the reactions yielded the same three (**2a**, **2b**, and **2c**)[8b] isomers as obtained earlier.[8b] Of them, **2b** and **2c** were produced predominantly and **2a** was obtained in trace amount in all cases (Table 1, entries a–d). While, Co- and Fe-mediated reactions afforded **2c** little more than **2b** (Table 1, entries a and b), Cu-mediated reaction produced **2c** in much higher amount (Table 1, entry c). In sharp contrast with these three cases (Table 1, entries a–c) and also the earlier one,[8b] low valent Sn-mediated reaction produced **2b** as the major product (Table 1, entry d). This suggests that each low valent metal mediator has its characteristic role regarding the stereo-selectivity in crotylation of **1**. The easy separation of the diastereomers **2a**–**c** by column chromatography enabled us to obtain each of them in homochiral form and determine the stereo-selectivity of each reaction. The fourth possible isomer (**2d**)[14] was obtained from **2c** following an oxidation–reduction protocol.[8h] Thus, PCC oxidation of **2c** yielded ketone **3** which was reduced with K-selectride to obtain **2d** (Scheme 3) in good yield and with absolute stereo-selectivity.

The formation of 2,3-*anti* addition products (**2b** and **2c**) in major amount in all these additions gave evidence that the reactions took place following Felkin–Anh model (Fig. 2).[15] However, the presence of 3,4-*syn*- and 3,4-*anti*- relationships, respectively, in these two major products (**2b** and **2c**) suggested the participation of Zimmerman–Traxler transition state[16] (Fig. 3) during the addition of crotylmetals. Presumably, in each case there has been a substantial degree of inter conversion between (*E*)-crotylmetal (**X**) that was predominantly formed initially from crotyl bromide (Fluka make, containing a mixture of *cis* and *trans*-bromide: 1:5) and (*Z*)-crotylmetal (**Y**) prior to the C–C bond formation. Hence, the differences in the formation of **2b** and **2c** in all four cases could be explained from the degree of inter conversion between (*E*)-crotylmetal (**X**) and (*Z*)-crotylmetal (**Y**) which was certainly governed by the low valent metal mediator involved.

To prepare **A**, compound (**2c**) was first silylated to obtain **4** in almost quantitative yield. Regio-selective hydroxylation at its terminal olefin afforded **5**[17] in good yield. Benzoylation of **5** and deketalization of the resulting benzoate **6** in acidic condition gave 1,2-diol **7**.[18] This was subjected to $NaIO_4$ cleavage to produce aldehyde **8**. Wittig olefination of **8** yielded olefin **9** in good yield which was saturated on catalytic hydrogenation to afford **10**. This was debenzoylated to give **11**.[19] PCC oxidation of **11** gave aldehyde **12** which without being purified further was desilylated to afford the relatively unstable lactol **13**. This was quickly oxidized with PCC to furnish *trans*-oak** lactone (**I**)[20] (Scheme 3) whose spectral and optical data were in conformity with the reported ones.[7a]



Scheme 2. Crotylation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde(**1**). Reagents: (i) *E*-Crotylbromide, Zn/$CuCl_2.2H_2O$, $CoCl_2.6H_2O$ or $FeCl_3$ or $SnCl_2.2H_2O$, THF.



Scheme 3. Synthesis of *trans*-oak lactone (**A**). Reagents and conditions: (i) PCC, CH_2Cl_2, rt; (ii) K-selectride, THF, −78 °C; (iii) TBDPSCl, imidazole, CH_2Cl_2; (iv) $Me_2S{\cdot}BH_3$, hexane, $NaOH–H_2O_2$; (v) BzCN, TEA, CH_2Cl_2; (vi) 80% aq CF_3COOH, 0 °C, CH_2Cl_2; (vii) $NaIO_4$, $MeCN/H_2O$ (3:2); (viii) *n*-$C_3H_7PPh_3^+Br^-$, *n*-BuLi, THF, −60 °C; (ix) 10% Pd–C, EtOH, 0 °C; (x) K_2CO_3, MeOH, rt; (xi) TBAF, THF.

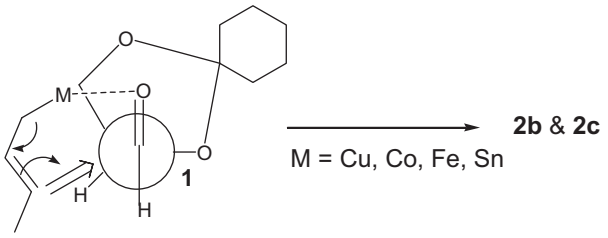


Figure 2. Fekin-Anh model for crotylmetal addition to **1**.

4. Conclusion

In summary, (4*S*,5*R*)-*trans*-oak lactone (**A**), a representative example of chiral *trans*-β,γ-disubstituted γ-lactone has been synthesized using Barbier type crotylations of **1** in wet media mediated with four different low valent metals.[11] All these crotylation reactions (Scheme 2 and Table 1) produced **2** in good yields, but with varied stereo-selectivity, showing the formation of **2b**/**2c** predominantly and **2a** in trace amount. The fourth isomer **2d** was later prepared from **2c** using an oxidation-reduction protocol.[8h] Finally, one (**2c**) of the major crotylation products was exploited to prepare **A**. Evidently, our route is shorter, more straightforward, and practically more viable compared to a reported approach[7a] for the synthesis of the same molecule **A** staring from **1**. Understandably, employing the same reaction protocol with **2a**, **2d**, and **2b** would lead to the synthesis of other three diastereomers, namely, (4*R*, 5*S*)-*trans*-(***ent*-A**), (4*S*, 5*S*)-*cis*- (**B**), and (4*R*, 5*R*)- *cis*-(***ent*-B**), respectively. Hence, the moderate selectivity of these crotylations of **1** and the easy separation of the diastereomers (**2a-c**) by column chromatography together enhanced the possibility of obtaining all four oak lactone stereoisomers and thereby attaining stereodivergence in this route.

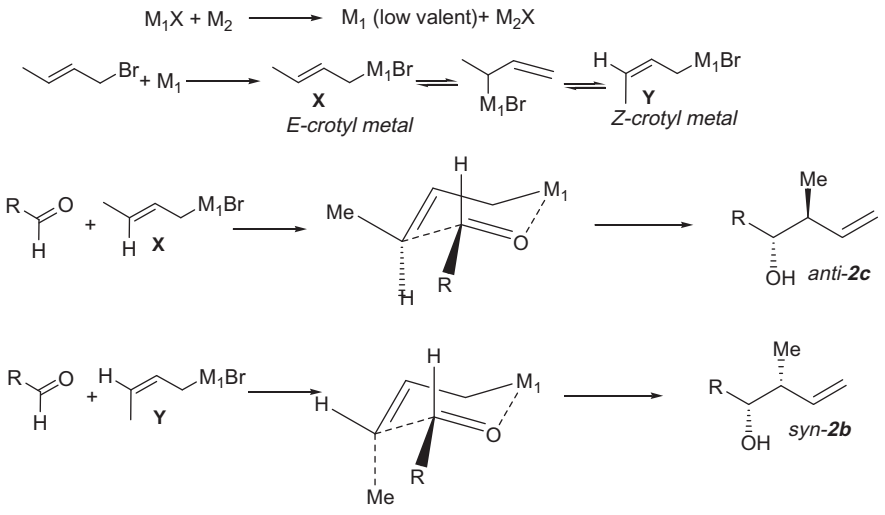


Figure 3. Zimmerman-Traxler model for crotylmetal addition to **1**.

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13. General procedure for crotylation of **1** employing bimetal redox strategy: To a cooled (10 °C) solution of **1** (1.7 g, 10 mmol) in THF (50 mL) metal salt [$CuCl_2.2H_2O$ (4.25 g, 25 mmol) or $CoCl_2.6H_2O$ (5.95 g, 25 mmol) or anhydrous $FeCl_3$ (3.24 g, 20 mmol) or $SnCl_2.2H_2O$ (4.5 g, 20 mmol)] was added. The mixture was stirred gently for 5 min. To this stirred suspension first crotyl bromide (2.7 g, 20 mmol) was added. Then Zn dust (1.63 g, 25 mmol) was added to it in portions over a period of 20 min. The reaction mixture was gradually brought to room temperature with stirring over a period of 1.5 h and then stirred further at the same temperature for an additional period as shown in Table 1 till the total disappearance of the starting material (TLC). It was then treated successively with water (25 mL) and EtOAc (50 mL). The mixture was stirred for 10 min more and then filtered. The filtrate was treated with 2% aqueous HCl to dissolve a little amount of suspended particles. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with water, brine, and then dried. Solvent removal under reduced pressure afforded residue which on column chromatography (silica gel, 0-20% EtOAc/Hexane) gave three diastereomers **2a**[8b] [29 mg while using $FeCl_3$/Zn; 74 mg while using $CuCl_2.2H_2O$/Zn; 66 mg while using $CoCl_2.2H_2O$/Zn; 129 mg while using $SnCl_2.2H_2O$/Zn], **2b**[8b] [950 mg while using $FeCl_3$/Zn; 525 mg while using $CuCl_2.2H_2O$/Zn; 835 mg while using $CoCl_2.2H_2O$/Zn; 1.42 g while using $SnCl_2.2H_2O$/Zn], and **2c**[8b] [984 mg while using $FeCl_3$/Zn; 1.18 g while using $CuCl_2.2H_2O$/Zn; 856 mg while using $CoCl_2.2H_2O$/Zn; 267 mg while using $SnCl_2.2H_2O$/Zn]
14. Compound **2d**: $[\alpha]_D^{23}$ −12.3 (*c* 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.1 (d, *J* = 6.8 Hz, 3H), 1.4-1.6 (m, 10H), 2.02 (m, 1H), 2.28-2.32 (m, 1H), 3.29 (dd, *J* = 4.6, 6.8 Hz, 1H), 3.70-3.77 (m, 1H), 3.98 (dd, *J* = 6.4, 8.0 Hz, 1H), (4.10-4.15 (m, 1H), 5.01-5.07 (m, 2H), 5.6-5.8 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.7, 23.7, 23.9, 25.0, 34.8, 36.0, 42.2, 66.1, 74.5, 76.2, 109.5, 115.2, 140.4. Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.23; H, 9.56.
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17. Compound **5**: $[\alpha]_D^{24}$ +23.2 (*c* 1.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.35-1.52 (m, 12H), 1.61-1.72 (m, 2H), 3.36-3.48 (m, 2H), 3.62 (t, *J*=7.2 Hz, 1H), 3.71 (dd, *J* = 2.2 and 6.4 Hz, 1H), 3.86-3.93 (m, 1H), 4.09-4.16 (m, 1H), 7.25-7.47 (m, 6H), 7.66-7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.2, 19.3, 23.7, 23.8, 25.0, 26.9, 33.8, 34.5, 35.2, 35.9, 60.7, 67.4, 75.6, 77.5, 108.9, 127.3, 127.4, 129.5, 129.6, 133.4, 133.5, 135.8. Anal. Calcd. for $C_{29}H_{42}O_4Si$: C, 72.15; H, 8.77. Found: C, 72.34; H, 8.52.
18. Compound **7**: $[\alpha]_D^{24}$ +6.72 (c 1.61, $CHCl_3$); ^{1}H NMR: 1.03 (d, *J* = 6.98 Hz, 3H), 1.09 (s, 9H), 1.61-1.66 (m, 1H), 1.9-2.0 (m, 2H), 2.42 (bs, 2H), 3.53-3.61 (m, 1H), 3.69-3.80 (m, 3H), 4.13-4.19 (m, 2H), 7.25-7.45 (m, 9H), 7.65-7.71 (m, 4H), 7.92-7.97 (m, 2H); ^{13}C NMR: 15.1, 19.4, 27.0, 31.3, 34.0, 63.4, 63.9, 72.8, 77.4, 127.4, 127.6, 128.1, 129.3, 129.7, 130.1, 132.6, 133.2, 135.8, 166.5. Anal. Calcd. for $C_{30}H_{38}O_5Si$: C, 71.11; H, 7.56. Found: C, 71.33; H, 7.39.
19. Compound **11**: $[\alpha]_D^{24}$ + 4.6 (c 1.4, $CHCl_3$); ^{1}H NMR: 0.76 (t, *J* = 3.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.08 (m merged with s, 13H), 1.41-1.46 (m, 4H), 1.50-1.54 (m, 1H), 1.97 (broad s, 1H), 3.50-3.58 (m, 3H), 7.37-7.44 (m, 6H), 7.68-7.73 (m, 4H); ^{13}C NMR: 13.9, 15.5, 19.5, 22.5, 27.1, 28.0, 32.6, 34.3, 34.5, 60.6, 77.4, 127.3, 127.4, 129.4, 129.5, 124.1,134.5, 136.0. Anal. Calcd. for $C_{25}H_{38}O_2Si$: C, 75.32; H, 9.61. Found: C, 75.11; H, 9.77.
20. Compound **I**: $[\alpha]_D^{24}$ + 93.5 (c 0.25, $CHCl_3$); Lit[7a] $[\alpha]_D^{24}$ + 93 (c 0.2, $CHCl_3$). ^{1}H NMR: 0.91 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.19-1.65 (m, 6H), 2.16-2.21 (m, 2H), 2.62-2.71 (m. 1H), 3.96-4.02 (m, 1H). ^{13}C NMR: 14.3, 17.2, 22.7, 27.5, 33.8, 36.0, 37.9, 87.6, 176.7.