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Highly diastereoselective alkylation of vicinal dianions of chiral succinic acid derivatives: a new general strategy to (*R*)-β-arylmethyl-γ-butyrolactones

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Abstract—The vicinal dianions derived from chiral succinic acid derivatives, 1,4-bis[(4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]butane-1,4-dione and 1,4-bis[(4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]butane-1,4-dione react with arylmethyl bromides with high diastereo- and regio-selectivity to provide the corresponding chiral α-arylmethylated succinic acid derivatives; the (*R*)-products are converted into (*R*)-β-arylmethyl-γ-butyrolactones and (*R*)-α-arylmethyl-γ-butyrolactones.

Succinic acid derivatives are of importance because they can serve as four-carbon building blocks in organic synthesis. Having considered the basic skeleton of many classes of compounds such as lignans[1] possessing a γ-butyrolactone or tetrahydrofuran nucleus, it was found that such compounds consisting of a four-carbon unit could be considered as a carbon backbone derived from succinic acid derivatives. Therefore, considerable attention has been focused on the synthetic utilities of succinic acid derivatives.[2] In connection with our recent reports on the synthetic utilities of vicinal dianions derived from α-aroylsuccinic esters as useful reagents for the synthesis of α-arylideneparaconic esters and furofurans,[3] it is of interest to extend our investigation on new synthetic strategies to chiral γ-butyrolactone frameworks, especially some bioactive naturally occurring γ-butyrolactone lignans. We therefore studied the generation and diastereoselective alkylation of vicinal dianions derived from chiral succinic acid derivatives.[4] This study is focused on a new general diastereoselective synthesis of chiral β-arylmethylated γ-butyrolactones, which are versatile intermediates for the asymmetric syntheses of lignans. Several synthetic approaches for the optically active β-arylmethyl-γ-butyrolactones have been published.[5] The vicinal dianion **2a** was generated by reacting chiral succinic acid derivative **1a** with 2 equiv of LDA in THF at −78 °C for 1 h. Treatment of **2a** with 1 equiv of benzyl bromide at −78 °C for 5 h afforded the benzylated product **3a** in 50% yield as a single diastereomer, together with the recovered starting material **1a** in 41% yield. A better yield of **3a** (75%) was obtained, when 2.2 equiv of benzyl bromide were employed under the same conditions. It is noteworthy that the reaction using 1 or 2 equiv of benzyl bromide gave only the monobenzylated product **3a**.[6,7] The (*S*)-configuration at the new stereocenter of compound **3a** was confirmed by converting into the corresponding known (*S*)-α-benzylsuccinic acid.[8] When the reaction was carried out in the presence of DMPU and slowly warmed up from −78 °C to room temperature overnight, a complex mixture of products was obtained as revealed by TLC and ^{1}H NMR data. Having the standard conditions, we next investigated the reactions of the vicinal dianion **2a** with methyl iodide and allyl bromide. The products **3b** and **3c** were also obtained as a single diastereomer in moderate yields as indicated in Table 1 (entries 2 and 3, Scheme 1).

Similarly, the vicinal dianion **2b** could be generated from **1b** and reacted with arylmethyl bromides (2.2 equiv) at −78 °C for 5 h to give arylmethylated products **4a**–**c** in moderate yields (Table 1, entries 4–6). The reaction proceeded with high diastereo- and regio-selectivities; all compounds **4a**–**c** were obtained as a single diastereomer. The configuration of the new chiral center of **4b** was proved to be (*R*) by single crystal X-ray diffraction

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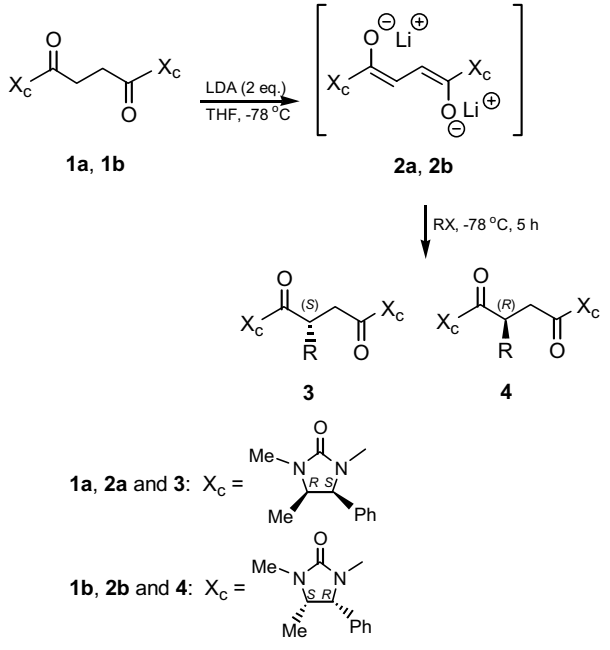
Table 1. Alkylation of vicinal dianions **2a** and **2b**

Entry	1	RX	3[b] or 4[b], R =	Yield (%)[a]
1	**1a**	$PhCH_2Br$	**3a**, $PhCH_2$	75
2	**1a**	MeI	**3b**, Me	48
3	**1a**	$CH_2{=}CHCH_2Br$	**3c**, $CH_2{=}CHCH_2$	49
4	**1b**	3,4-$MeOPhCH_2Br$	**4a**, 3,4-$MeOPhCH_2$	53
5	**1b**	3-$MeOPhCH_2Br$	**4b**, 3-$MeOPhCH_2$	67
6	**1b**	3,4-$CH_2(O)_2PhCH_2Br$	**4c**, 3,4-$CH_2(O)_2PhCH_2$	67

[a] Isolated yields. All compounds were fully characterized by ^1H NMR, ^{13}C NMR, MS, and CHN analyses or HRMS.
[b] The specific rotation values, $[\alpha]_D^{28}$ of **3a–c** and **4a–c** are as follows: **3a**; +127.84 (*c* 0.51, MeOH); **3b**, +117.45 (*c* 0.55, $CHCl_3$); **3c**, +107.50 (*c* 0.64, $CHCl_3$); **4a**, −45.02 (*c* 0.31, $CHCl_3$); **4b**, −64.57 (*c* 0.70, $CHCl_3$); **4c**, +46.85 (*c* 0.29, $CHCl_3$).



Scheme 1.

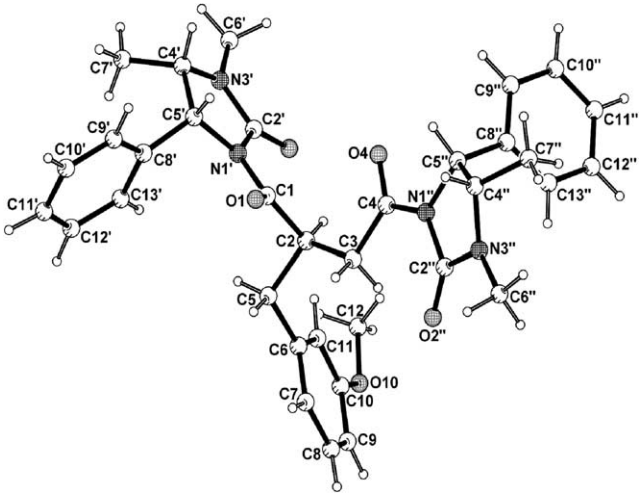


Figure 1. Crystal structure of compound **4b**.

analysis[9] (Fig. 1), which suggested the simple model for the stereochemical course of the benzylation of the vicinal dianion **2b** shown in Figure 2.

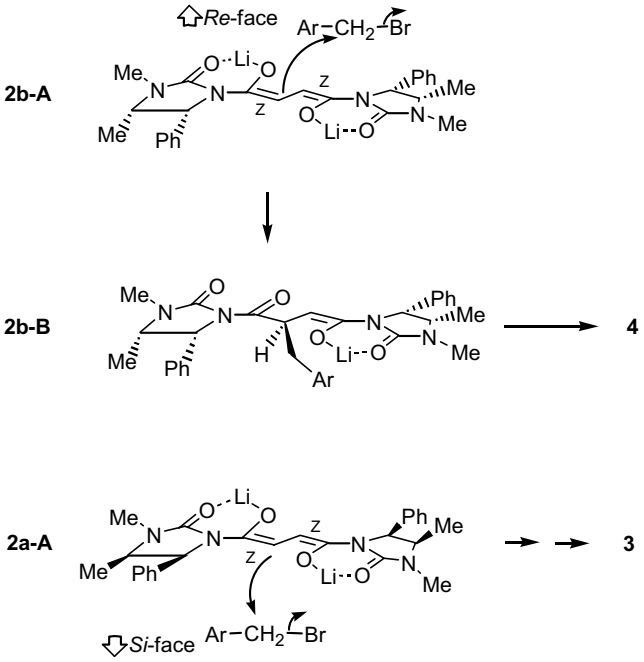
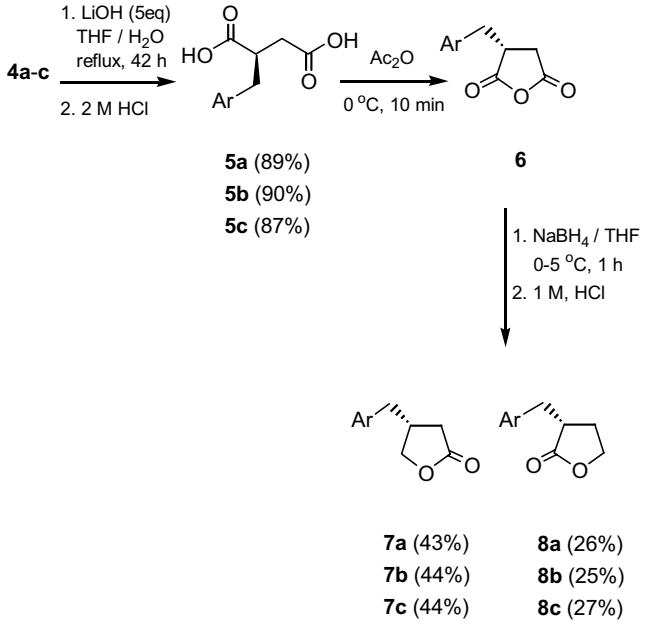


Figure 2. Proposed models for the stereochemical course of the alkylation of the vicinal dianions **2a** and **2b**.

Based on the evidence that Li-chelated (*Z*)-enolates were formed upon treatment of 1-acyl-2-imidazolidinones with LDA,[10] the vicinal dianion intermediate **2b** is proposed to exist in the (*Z*,*Z*)-configuration possessing the defined six-membered ring chelate structure **2b–A**. In the formation of **4a–c**, the arylmethyl bromides would approach from the *Re*-face of the vicinal dianion **2b–A** to avoid the steric repulsion with phenyl and methyl groups leading to an intermediate **2b–B**. The second arylmethylation of **2b–B** does not occur due to the steric hindrance between the α-arylmethyl and the chiral auxiliary phenyl groups. As similar model **2a–A** may also be applied to the alkylation of the vicinal dianion **2a**, in which the alkylating agent approaches from the *Si*-face (Fig. 2).

Having established that highly diastereoselective alkylation of the vicinal dianion **2b** furnishes the single diastereomer of compounds **4a–c** possessing the (*R*)-configuration at the α-carbon, we turn our attention to the preparation of (+)-β-arylmethyl-γ-butyrolactones. This could be accomplished by a hydrolysis–anhydride



Scheme 2.

formation–reduction sequence, starting from chiral succinic acid derivatives **4** (Scheme 2).

Thus, hydrolyses of **4a–c** employing LiOH (5 equiv) in aqueous THF under reflux for 40–42 h provided the corresponding succinic acid derivatives **5a–c** in good yields after acidic work-up.[11] Treatment of these acids with excess Ac_2O at 0 °C afforded the corresponding acid anhydrides **6** in quantitative yields. Reduction of **6** with $NaBH_4$ in THF at 0–5 °C for 1 h afforded the mixtures of the expected (*R*)-β-arylmethyl-γ-butyrolactones **7**[12] and (*R*)-α-arylmethyl-γ-butyrolactones **8**,[12] which could be separated by chromatography on silica gel.

In conclusion, we have described a general entry to an enantioselective synthesis of (*R*)-β-arylmethyl-γ-butyrolactones. The method involves highly regio- and diastereoselective arylmethylations of the vicinal dianions derived from chiral succinic acid derivatives, 1,4-bis[(4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]butane-1,4-dione and 1,4-bis[(4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimi-dazolidin-1-yl]butane-1,4-dione. It is anticipated that the methodology described herein will find a number of useful applications in asymmetric synthesis of lignans.

Acknowledgements

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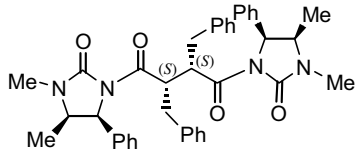
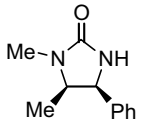
6. Treatment of **1a** with 1 equiv of LDA, followed by reacting with 1 or 2 equiv of benzyl bromide under the standard conditions provided a low yield of the expected product **3a**.
7. Attempts to prove the presence of the vicinal dianion **2a** by quenching with D_2O were unsuccessful. No deuterium incorporation was observed as revealed by ^1H NMR and MS. In spite of these results, it was still assumed that the

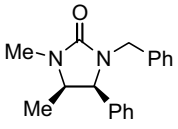
vicinal dianion **2a** was generated under the conditions described. This may be due to a strong H-bonded complex between diisopropylamine and the dilithiated derivative. Such interaction effecting incomplete deuteration of the generated lithium derivative was reported by Seebach (Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta*, **1985**, *68*, 1373–1393). The reaction of the vicinal dianion **2a** with 2.2 equiv of benzyl bromide at −78 °C to room temperature overnight (12–16 h) afforded dibenzylated product **9** in 20–30% yields together with 30–40% yields of the chiral auxiliary, (4*S*,5*R*)-(+)-1,5-dimethyl-4-phenyl-2-imidazolidinone and compound **11**. The formation of **9** supported the presence of the vicinal dianion **2a**. Compound **9** was obtained as a single diastereomer and its structure is proposed as shown below. The results also indicated that the vicinal dianion **2a** slowly decomposed during warming from −78 °C to rt to provide **10** and **11**.



9, $[\alpha]_D^{29}$ = +146.3 (*c* 1.226, $CHCl_3$)



10



11

8. $[\alpha]_D^{31}$ (observed) −20.19 (*c* 2.08, EtOAc). Lit. $[\alpha]_D^{25}$ −27 (*c* 2, EtOAc); Cohen, S. G.; Milovanovic, A. *J. Am. Chem. Soc.* **1968**, *90*, 3495–3502.
9. Crystal data for **4b**: $C_{34}H_{38}N_4O_5$, MW = 582.70, orthorhombic, space group $P2_12_12_1$, $a = 8.1187(5)$, $b = 10.1120(5)$, $c = 38.5830(5)$ Å, $V = 3167.5(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.222$ Mg/m^3. A total of 2,115 unique reflections (1,724 observed, $|F_o| > 4\sigma|F_o|$) were measured at room temperature from a $0.30 \times 0.15 \times 0.15$ mm^3 colorless crystal using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) on a Bruker–Nonius kappaCCD diffractometer. The crystal structure was solved by direct methods using SIR-97, and then all atoms except hydrogen atoms were refined anisotropically on F^2 using SHELXL-97 to give a final *R*-factor of 0.0493 and $wR = 0.1130$ (all data). Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, ENGLAND (CCDC 216625).
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11. The chiral auxillary was recovered in 85–95% yields and could be reused without loss of diastereoselectivity.
12. Specific rotation values for **7a**–**c** and **8a**–**c**. **7a**: $[\alpha]_D^{28}$ +8.75 (*c* 0.32, $CHCl_3$); Lit.[5j]: $[\alpha]_D^{24}$ +8.3 (*c* 1.33, $CHCl_3$). **7b**: $[\alpha]_D^{31}$ +7.31 (*c* 0.74, $CHCl_3$); Lit.[5k]: $[\alpha]_D^{20}$ +6.41 (*c* 2.08, $CHCl_3$). **7c**: $[\alpha]_D^{30}$ +5.12 (*c* 1.13, $CHCl_3$); Lit.[5j] $[\alpha]_D^{20}$ +5.2 (1.14, $CHCl_3$). **8a**: $[\alpha]_D^{28}$ −58.00 (*c* 0.20, $CHCl_3$). **8b**: $[\alpha]_D^{31}$ −53.78 (*c* 0.48, $CHCl_3$). **8c**: $[\alpha]_D^{28}$ −51.34 (*c* 0.26, $CHCl_3$).