Tetrahedron Letters 51 (2010) 3728–3731

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile synthesis of asymmetric quaternary centers based on diastereoselective protection of the carbonyl group at the symmetrical position

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ARTICLE INFO

Article history:
Received 17 April 2010
Revised 1 May 2010
Accepted 7 May 2010
Available online 12 May 2010

ABSTRACT

The C2-side chain hydroxyl group of 1,3-cycloalkanedione discriminates between two ketones depending on its chirality. It chooses one ketone to form hydrogen bond with the oxygen atom of the TBDPS–oxymethyl group, but chooses the other ketone upon conversion to the isopropyl acetal. Two optically pure diastereomers, whose absolute configuration at the angular position is opposite for each other, were thus synthesized from this single chiral source through simple operations. This method may be applied for the synthesis of a variety of compounds with asymmetric quaternary centers.

Chiral quaternary centers at the angular position are commonly found in biologically active compounds. It is thus critical subject in organic synthesis that general and efficient methods be devised to prepare chiral quaternary centers.

Among the reported methods for the stereoselective synthesis of quaternary carbon centers,[1] the desymmetrization of the symmetrical compound[2] is one of useful methodologies because of its efficiency and easy preparation of starting materials. Principal methods of the desymmetrization for the construction of asymmetric carbon centers which do not contain carbon–hydrogen bonds include (1) enzymatic reaction,[3] (2) catalysis by chiral metal–ligand complex,[4] (3) catalysis by organocatalyst,[5] and (4) internal asymmetric induction.[6] Many reactions promoted by chiral metal–ligand complexes and organocatalysts have been reported, but only limited number of reports exist on reactions by internal asymmetric induction. Briefly, if functional group X in **1** (Fig. 1) can discriminate the other functional groups, which are symmetric with respect to each other, to selectively give compound **2a** or **2b** under independent reaction conditions, then there might be a useful method to prepare both enantiomers with a quaternary carbon center. In this Letter, we introduce a practical and widely applicable method to prepare two diastereomers having chiral quaternary carbon center, whose absolute configuration is opposite for each other, through the chiral discrimination of the symmetrical 2,2-disubstituted-1,3-cycloalkanedione utilizing a remote chiral source at C2-side chain.

In agreement with this basic principle, we assumed that the hydroxyl group in **3** would discriminate two carbonyl groups depending on its chirality. Among four possible diastereomers **4a**–**d**, axial attack of the hydroxyl group yields **4a** and **4b** as major products upon consideration of both stereoelectronic effect and the observation that the cis-fused ring is usually more stable than the trans-fused one in a bicyclo[4.3.0] ring system. In compound **4a**, a hydrogen bond is expected between the hydroxyl group and the ether oxygen atom. This bond is strong enough to retain its configuration; therefore, **4a** will be predominantly produced over **4b**. Conversely, if the acetal moiety is rebuilt without steric repulsion between side chains, **4a** may yield **5b** as a major product because of the equilibrium that might occur between **4a** and **4b** through **3** (Fig. 2).

The substrates **11**–**17** were synthesized as shown in Scheme 1. Namely, 1,3-cyclohexanedione (**6**) or 1,3-cyclopentanedione (**7**) and (*R*)-2,2-dimethyl[1,3]dioxolane-4-carbaldehyde (**8**) were subjected to cascade Knoevenagel-hydrogenation reaction developed by Ramachary et al.[5l] to afford the common intermediates **9** or **10**. For the compound **9**, racemization during the reaction was not observed at all, as confirmed by chiral HPLC analysis.[7] The introduction of the substituent at C2 was carried out by Michael reaction with ethyl acrylate (for **11** and **17**), alkylation with halides in the presence of DBU[9] (for **13** and **14**), and Pd-catalyzed allylation reaction (for **12**, **15**, and **16**) (Scheme 1).

In our initial investigation, we selected the compound **11**, which has the ethoxycarbonyl-ethyl group as C2-substituent. Contrary to expectation, hydrolysis of the acetal group yielded acetal **18** as a

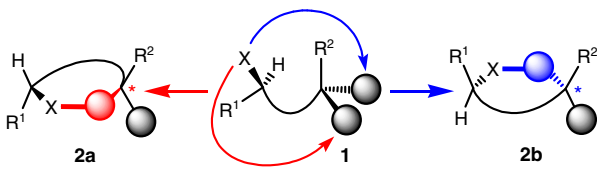

Figure 1. Representation of the chiral discrimination using a remote chiral source.

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doi:10.1016/j.tetlet.2010.05.010

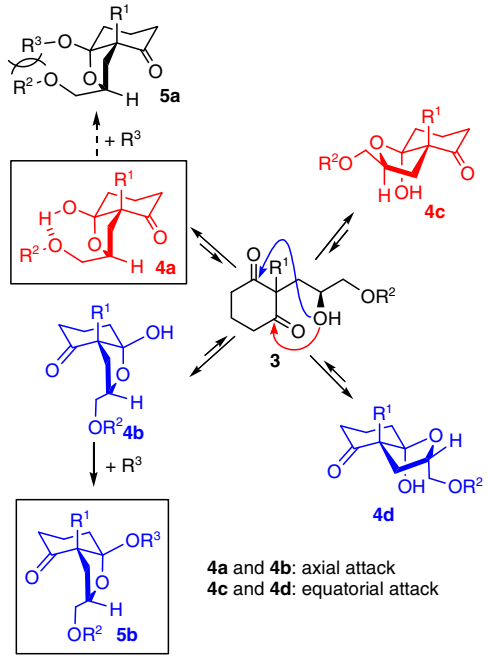
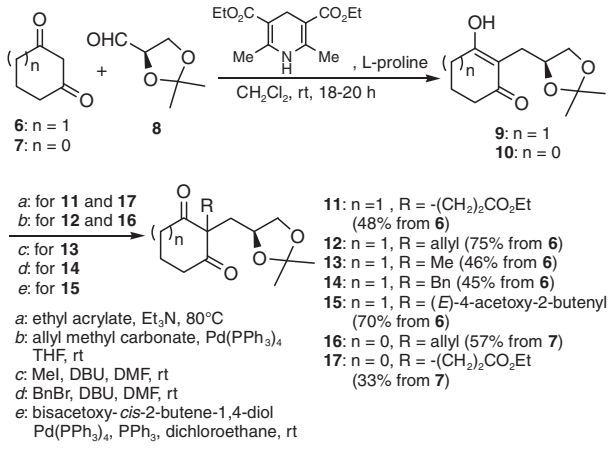


Figure 2. General concept for chiral discrimination of synthon **3** into products **4a** and **5b**.

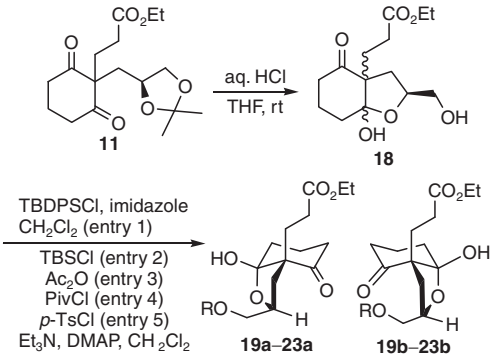


Scheme 1. Synthesis of the substrates **11**–**17**.

mixture of diastereomers. However, we were pleased to find that the resulting primary hydroxyl group was converted into the corresponding TBDPS (*tert*-butyldiphenylsilyl) ether to afford **19a** as a major product (**19a**:**19b** = 96:4), observed in $CDCl_3$ by ^1H NMR spectroscopy (Table 1, entry 1).

Since $H_{3\alpha}$ and the carbonyl group at C4 in the compound **19a** were almost coplanar in each, the chemical shift of $H_{3\alpha}$ in ^1H NMR spectrum[8] was observed at low-field (2.68 ppm) due to the deshielding effect by the carbonyl group as compared with that of $H_{3\beta}$ (1.83–1.88 ppm). The structure of **19a** was determined by NOESY spectroscopy[8] and the presence of NOE between H_a and H_b is noteworthy to support this structure (Fig. 3). The presence of intramolecular hydrogen bond was confirmed by the sharp singlet and relatively downfield (4.39 ppm) in ^1H NMR spectrum,[8] which corresponds to the hydroxyl proton and the chemical shift showed essentially no change when ^1H NMR spectra were measured at different concentrations in $CDCl_3$.[8] The bulkiness of the R substituent did not affect the diastereomeric ratios (Table 1, entries 1 vs 2 and 3 vs 4). However, the ratios decreased significantly

Table 1
Diastereoselectivity change induced by the hydroxymethyl group substituent[10]



Entry	Product (R)	Yield (%)	dr (**a**:**b**)[a]
1	**19a**,**b** (TBDPS)	88	96:4
2	**20a**,**b** (TBS)	86	>99:1
3	**21a**,**b** (Ac)	85	75:25
4	**22a**,**b** (Piv)	94	75:25
5	**23a**,**b** (Ts)	78	67:33

[a] Dr was determined from the integration value of the ^1H NMR spectrum.

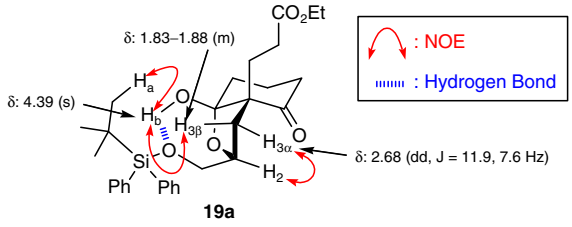
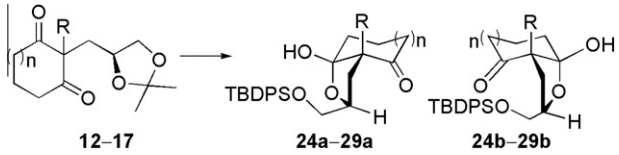


Figure 3. Summary for ^1H NMR and NOESY spectra of the compound **19a**.[8]

Table 2
Diastereoselective intramolecular acetalization reactions of **12**–**17**[a]



Entry	SM (*n*)	Product (R)	Yield[b] (%)	dr (**a**:**b**)[c]
1	**12** (1)	**24a**,**b** (allyl)	78	97:3
2	**13** (1)	**25a**,**b** (Me)	71	96:4
3	**14** (1)	**26a**,**b** (Bn)	97	95:5
4	**15** (1)	**27a**,**b** ((*E*)-4-acetoxy-2-butenyl)	73	96:4
5	**16** (0)	**28a**,**b** (allyl)	91	96:4
6	**17** (0)	**29a**,**b** (-$(CH_2)_2CO_2Et$)	87	93:7

[a] Reagents and conditions: (1) aq HCl, THF, rt; (2) TBDPSCl, imidazole, CH_2Cl_2, rt.
[b] Overall yield.
[c] Dr was determined by the integration value of the ^1H NMR spectrum.

when electron-withdrawing groups, which may weaken hydrogen bonds, were incorporated (Table 1, entries 3–5). Moreover, it was found that compounds **19a** and **24a** (Table 2, entry 1) were essentially single isomers, as determined by ^1H and ^{13}C NMR spectra in $CDCl_3$, whereas the same compounds formed diastereomer mixtures in CD_3CN–D_2O (9:1) (**19a**:**19b** and **24a**:**24b** = 3:1).[8,10] This results indicate the importance of hydrogen bond in maintaining the configuration.

Discrimination of the carbonyl groups was found to be quite general. Compounds with an allyl, methyl, benzyl, or (*E*)-4-acet-

oxy-2-butenyl group at the C3a position (**24a**–**27a**) were produced with more than 95:5 selectivity (Table 2, entries 1–4). Five-membered analogues **28a** and **29a** were also afforded in high diastereoselectivity (Table 2, entries 5 and 6).

Next, we challenged the inversion of absolute configuration at the angular position. As expected, the ratios of produced diastereomers changed according to the size of alcohols during acetal formation. The highest yield of **32b** was obtained with 2-propanol and triisopropyl orthoformate, and $Ce(OTf)_3$ as a catalyst[11] (Table 3, entry 3). The chemical shifts of $H_{3\alpha}$ in ^1H NMR spectra of the compounds **32a** and **32b** were observed again at low-field (**32a**: 2.79 ppm, **32b**: 2.93 ppm) as compared with those of $H_{3\beta}$ (**32a**: 1.52 ppm, **32b**: 1.89 ppm) and the stereochemistry of the both compounds were determined by NOESY spectroscopy shown in Figure 4.[8]

Under identical reaction conditions, quasi-similar degrees of diastereoselectivity inversion were observed for compounds **19a** (Table 3, entry 4) and **25a**–**27a** (Table 3, entries 5–7), which have different R^1. We therefore confirmed that the inversion would be applied to a wide variety of substrates possessing different functional group at C3a (R^1).

In conclusion, we have established a simple, efficient method to synthesize two types of diastereomers **19a**, **24a**–**29a**, and **32b**–**36b** with opposite absolute configurations at the angular position from a single chiral source in high selectivity.[12] Expensive chiral sources are thus not required and it can be applied to a variety of 1,3-cyclohexanedione and 1,3-cyclopentanedione derivatives because diastereoselectivity is independent on the C2 substituent in the starting material.

Because desymmetrization reactions based on carbon–carbon bond formation are irreversible, it seems likely that synthesizing the chiral center having different absolute configuration from single chiral molecule requires the special devices. Desymmetrization reactions of 3,3-disubstituted-1,4-cyclohexadiene derivatives[2d,6b–e,g–i] by catalytic reaction or chiral induction have been reported. However, the fundamental difference between our method and those examples is reversibility. Our method is based on a carbon–oxygen bond formation and can be regarded as the diastereoselective protection of the carbonyl group at the symmetrical position. The protected carbonyl group reverts back to the carbonyl group when necessary and is transformed to another functional group. Although the diastereoselectivity in the most examples by internal asymmetric induction were achieved by kinetic control, it is noteworthy that the diastereoselectivity at hemiacetal synthesis in our method was controlled by the thermodynamic stability among the possible compounds. This method may be applied to the synthesis of a wide variety of compounds with asymmetric quaternary carbon centers. Further applications of this method to the synthesis of a wide variety of compounds with asymmetric quaternary carbon centers. Further applications of this method to the synthesis of biologically active compounds are under investigation in our laboratory.

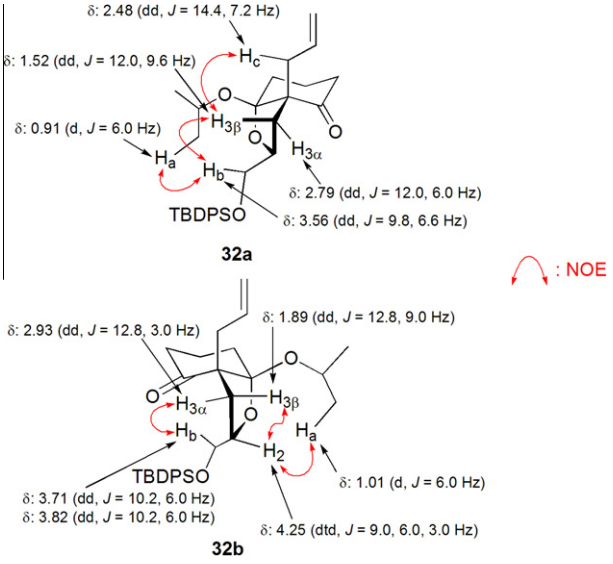
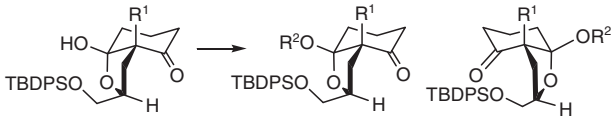


Figure 4. Summary for ^1H NMR and NOESY spectra of the compound **32a** and **32b**.[8]

Table 3
Diastereoselectivity inversion through intermolecular acetalization reactions



Entry	SM (R^1)	Product (R^2)	Yield (%)	dr (**a**:**b**)[d]
1[a]	**24a** (allyl)	**30a**,**b** (Me)	quant.	20:80
2[a]	**24a** (allyl)	**31a**,**b** (Et)	98	12:88
3[b]	**24a** (allyl)	**32a**,**b** (*i*-Pr)	91	8:92
4[c]	**19a** ($-(CH_2)_2CO_2Et$)	**33a**,**b** (*i*-Pr)	84	8:92
5[c]	**25a** (Me)	**34a**,**b** (*i*-Pr)	83	9:91
6[c]	**26a** (Bn)	**35a**,**b** (*i*-Pr)	92	13:87
7[c]	**27a** ((*E*)-4-acetoxy-2-butenyl)	**36a**,**b** (*i*-Pr)	79	9:91

Reagents and conditions: [a] $HC(OR^2)_3$ (3.0 equiv), $Ce(OTf)_3$ (10 mol %), R^2OH–toluene (1:1), rt, 3 h (entry 1: R^2 = Me, entry 2: R^2 = Et).
[b] $HC(Oi\text{-}Pr)_3$ (3.0 equiv), $Ce(OTf)_3$ (10 mol %), *i*-PrOH–toluene (1:1), rt for 3 h, then 70 °C for 1.5 h.
[c] $HC(Oi\text{-}Pr)_3$ (3.0 equiv), $Ce(OTf)_3$ (10 mol %), *i*-PrOH–toluene (1:1), 70 °C for 1 h (entries 4 and 5), for 16 h (entry 6), and for 1.5 h (entry 7).
[d] Dr was determined from the integration value of the ^1H NMR spectrum.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research (C) 19590001 and 21590001 from the Japan Society for the Promotion of Science (JSPS).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.010.

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