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Versatile, high 2,4-*syn* dialkyl diastereoselection in the radical debromination of α-bromo-α-methyl-δ-valerolactones with tri-*n*-butyltin hydride and a catalytic amount of triethylborane

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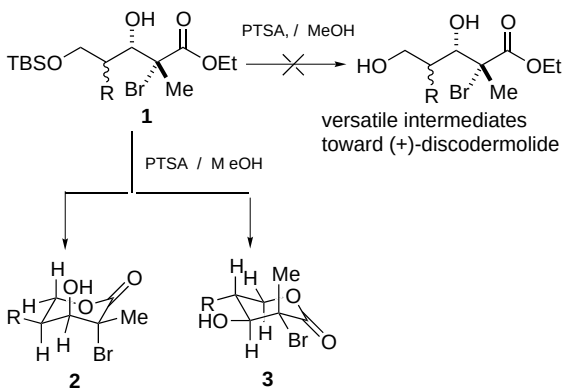
Abstract—An interesting 2,4-*syn* dialkyl diastereoselection has been observed in the radical debromination of α-bromo-α-methyl-δ-valerolactones. The reaction of 4-alkyl-2-bromo-3-hydroxy-2-methyl-5-pentanolides with Bu_3SnH and a catalytic amount of Et_3B gave, essentially, a single diastereomer with a 2,4-*syn* dialkyl relationship, independent of the orientation of the hydroxy substituent at C-3.

During our studies on the total synthesis of (+)-discodermolide we encountered a problem in which the acidic deprotection of the TBS function in 2,3-*syn* enantiomers **1**, which were intended for use in the preparation of the corresponding *syn*- and *anti*-propionate aldol adducts by a reliable methodology involving highly diastereoselective radical debromination,[1] resulted in a facile lactonization to give the δ-valerolactones, **2** and **3** (Scheme 1).[2] Since a variety of methods for converting stereochemically regulated δ-valerolactones to useful acyclic derivatives are available, an investigation of the debromination at the stage of δ-valerolactone was deemed to be the method of choice. Diastereoselection during radical reduction of not only acyclic but also the cyclic system[4,5] might be useful to synthetic organic chemists, because of the expected higher selectivity due to the ring system. The reductive cleavage of the carbon–bromine bond in an α-bromo-α-methylcyclohexanone derivative was reported to give the 2,4-*syn* dimethyl compound with moderate stereoselection under conditions using tri-*n*-butyltin hydride (Bu_3SnH) and a catalytic amount of the radical initiator azobisisobutyronitrile (AIBN).[3] We disclose herein a remarkable diastereoselection process which occurs during the radical debromination of α-bromo-δ-valerolactones.



Scheme 1.

The preparation of α-bromo-δ-valerolactones necessary for the present study was carried out by using our chiral oxazaborolidinone-promoted asymmetric aldol reaction of the racemic aldehyde **4** with bromo silyl nucleophile **5** in the presence of D-TsVal **6**. The reaction gave a 1:1 mixture of essentially enantiopure aldol adducts, **7** and **8**, with the so-called promoter control on acyclic stereoselection,[6] where the newly generated stereocenter (C-3) was controlled only by the chiral center of promoter **6**. Deprotection with *p*-toluenesulfonic acid (PTSA) in methanol gave the separable lactones, **2** and **3**, as shown in Scheme 2.

Debromination reactions of **2** and **3** took place smoothly in good yields by treatment with 5 mole equiv. of Bu_3SnH and a catalytic amount of Et_3B[7] in toluene at −78°C for 2 h. This reaction was accompanied with *striking diastereoselection* (∼100%) and the

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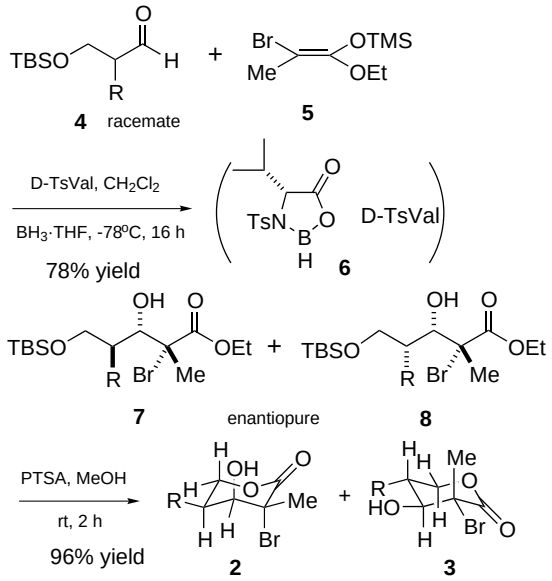
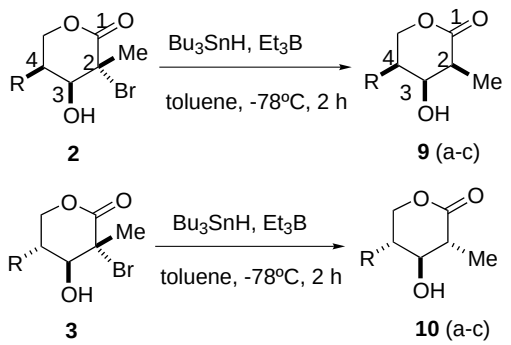


Scheme 2.

debrominated products, **9** and **10**,[8] were obtained from the reactions of **2** and **3**, respectively, with no detectable by-products, as shown in Scheme 3 and Table 1. The distinctive 2,4-*syn* selection, found in **9** and **10**, during the radical process appears to be affected only by the chiral center at C-4, completely independent of the direction of the hydroxy function at C-3. The stereochemical outcome can be rationalized on the basis of the avoidance of steric hindrance which can be attributed to the 1,3-interaction produced between the R substituent at C-4 and the incoming Bu_3SnH so that the hydride can approach the radical center at C-2 from the opposite side. The above rationalization, however, is not necessarily sufficient to account for the very high level diastereoselection.

In order to estimate the influence of bulkiness at C-3 on the diastereoselection, the hydroxy function of **2**-a and **3**-a was protected by a TMS group. The result is shown in Scheme 4. The radical debromination of **11** remained unchanged, compared with that of **2**-a, and a similar, high 2,4-*syn* selectivity was observed for **12** because of the same orientation of both substituents at C-3 and C-4. On the other hand, the selectivity in the reaction of



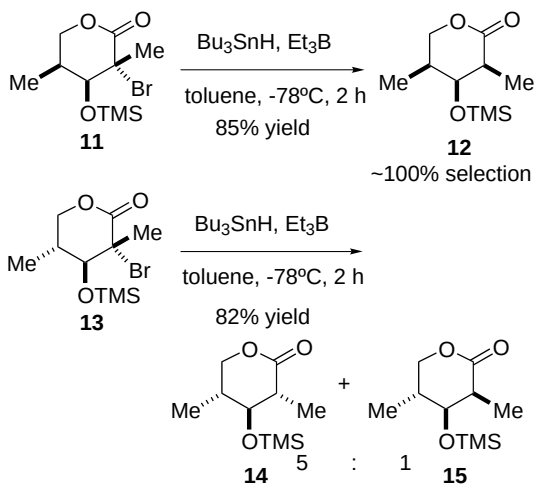
Scheme 3.

13 might be reduced because of the larger TMS substituent at C-3. We were actually able to trap the counter isomer, 2,4-*anti* **15**. However, a considerably large selection (5:1) was still observed. Thus, it is noteworthy that the orientation of the substituent at C-4 plays a major role in allowing a preferential approach of the hydride from the opposite side, compared with that at C-3. In the case of γ-lactones, such superior 2,4-*syn* diastereoselection could not be observed; the radical debromination reactions of isomers, **16** and **17**, having a configuration opposite that at C-2, resulted in the same low selectivity (2:1) of *syn*- and *anti*-products, **18** and **19**, which suggests that both reactions proceed via essentially the same transition state assembly (Scheme 5).

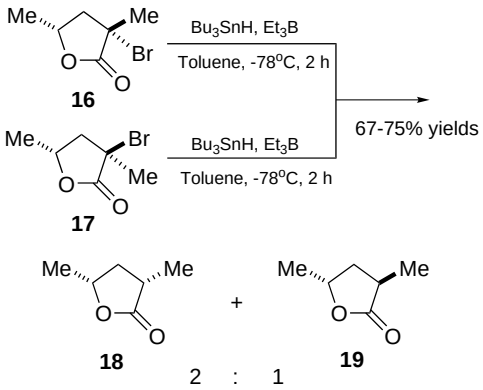
In conclusion, a very high level of diastereoselection was observed in the radical debromination of α-bromo-α-methyl-δ-valerolactones and the obtained selectivity reaches the level of practical use. In addition, the stereochemically regulated δ-valerolactones can be converted to versatile compounds having a simple 2,4-*syn* dialkyl unit, e.g. in the case of methyl groups at C-2 and C-4 after dehydroxylation at C-3, where they can subsequently be converted to a known chiral lactone[9] and the Prelog–Djerassi lactonic acid.[10] Furthermore, δ-valerolactones having 2,4-*syn* dialkyl units could be made generally available for use as precursors for acyclic segments through ring-opening with various

Table 1. Highly diastereoselective radical and debromination of α-bromo-α-methyl-δ-valerolactones, **2** and **3** (Scheme 3)

Entry	δ-valerolactones/R	Yields (%)	2,4-syn-diastereoselectivity (%)
1	Me (**2**-a)	78 (**9**-a)	~100
2	Pr (**2**-b)	75 (**9**-b)	~100
3	Bn (**2**-c)	91 (**9**-c)	~100
4	Me (**3**-a)	75 (**10**-a)	~100
5	Pr (**3**-b)	66 (**10**-b)	~100
6	Bn (**3**-c)	76 (**10**-c)	~100



Scheme 4.



Scheme 5.

types of reagents. A study of the reaction mechanism is currently underway.

Acknowledgements

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8. Physical data of products. **9**-a: $[\alpha]_D^{25}$ −6.0 (*c* 1.0%, $CHCl_3$). IR (neat) 3537, 1716 cm−1. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.07 (d, $J=6.8$, 3H), 1.40 (d, $J=7.1$, 3H), 1.97–2.07 (m, 1H), 2.20 (s, 1H), 2.44 (dq, $J=9.8$, 7.1, 1H), 3.30 (dd, $J=9.3$, 8.3, 1H), 3.83 (dd, $J=11.5$, 10.0, 1H), 4.32 (dd, $J=11.5$, 4.9, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.5, 13.7, 36.6, 44.2, 70.5, 75.9, 173.6. **9**-b: $[\alpha]_D^{24}$ −19.8 (*c* 0.96%, $CHCl_3$). IR (neat) 3426, 1728 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.95 (t, $J=7.1$, 3H), 1.38 (d, $J=7.1$, 3H), 1.21–1.45 (m, 4H), 1.87–1.93 (m, 1H), 2.21 (d, $J=4.9$, 1H), 2.49 (dq, $J=9.3$, 6.8, 1H), 3.37 (ddd, $J=9.0$, 7.1, 4.9, 1H), 3.95 (dd, $J=11.7$, 7.8, 1H), 4.40 (dd, $J=11.7$, 4.4, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.6, 14.1, 19.8, 31.4, 41.7, 43.8, 68.7, 75.1, 173.7. **9**-c: $[\alpha]_D^{18}$ −5.83 (*c* 1.2%, $CHCl_3$). IR (neat) 3428, 1728 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.38 (d, $J=6.8$, 3H), 2.07 (d, $J=4.9$, 1H), 2.19–2.28 (m, 1H), 2.54 (dq, $J=9.3$, 6.8, 1H), 2.56 (dd, $J=14.2$, 9.3, 1H), 3.03 (dd, $J=13.9$, 5.6, 1H), 3.74 (ddd, $J=9.3$, 7.1, 4.9, 1H), 3.93 (dd, $J=11.7$, 7.3, 1H), 4.26 (dd, $J=11.7$, 4.4, 1H), 7.18–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.5, 35.7, 43.6, 43.6, 68.1, 74.4, 126.8, 128.8, 129.0, 137.9, 173.6. **10**-a: $[\alpha]_D^{25}$ +1.0 (*c* 1.0%, $CHCl_3$). IR (neat) 3435, 1712 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.02 (d, $J=6.8$, 3H), 1.32 (d, $J=7.1$, 3H), 2.18–2.27 (m, 1H), 2.57 (dq, $J=7.1$, 3.2, 1H), 3.87 (s, 1H), 4.19 (dd, $J=11.0$, 5.8, 1H), 4.30 (dd, $J=11.0$, 11.7, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 12.8, 12.8, 33.8, 42.3, 70.2, 71.6, 173.1. **10**-b: $[\alpha]_D^{24}$ −2.5 (*c* 0.4%, $CHCl_3$). IR (neat) 3437, 1716 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.95 (t, $J=6.8$, 3H), 1.33 (d, $J=7.1$, 3H), 1.23–1.47 (m, 4H), 1.68 (s, 1H), 1.88–2.15 (m, 1H), 2.55 (dq, $J=7.3$, 3.0, 1H), 3.96 (s, 1H), 4.24 (dd, $J=11.0$, 6.1, 1H), 4.31 (dd, $J=11.7$, 11.0, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 12.9, 14.1, 19.8, 29.6, 38.6, 42.3, 69.5, 69.7, 173.5. **10**-c: $[\alpha]_D^{24}$ −35.0 (*c* 0.4%, $CHCl_3$). IR (neat) 3441, 1714 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.29 (d, $J=7.1$, 3H), 2.06 (d, $J=3.6$, 1H), 2.31–2.39 (m, 1H), 2.49 (dq, $J=7.1$, 2.9, 1H), 2.64 (dd, $J=13.7$, 6.6, 1H), 2.75 (dd, $J=13.7$, 8.8, 1H), 3.82 (s, 1H), 4.24 (dd, $J=11.0$, 5.9, 1H), 4.43 (t, $J=11.5$, 1H), 7.19–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 12.8, 33.8, 40.7, 42.3, 68.8, 69.3, 126.7, 128.7, 128.9, 138.3, 173.2.
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