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Stereoselective intramolecular coupling of diaroylacetates of (1*R*,1′*R*)-*exo*,*exo*′-3,3′-biisoborneol by oxidation with Br_2

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Abstract—The oxidative coupling of diaroylacetate derivatives prepared from (1*R*,1′*R*)-*exo*,*exo*′-3,3′-biisoborneol with NaH–Br_2 gave the corresponding intramolecularly coupled products stereoselectively. The major (*R*,*R*)-isomers thus obtained were transformed to (−)-Sesamin and (−)-Eudesmin.
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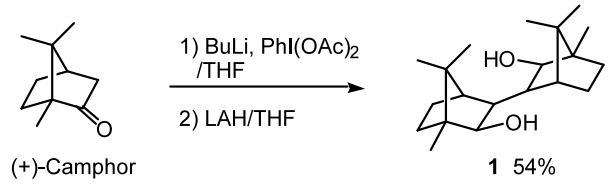
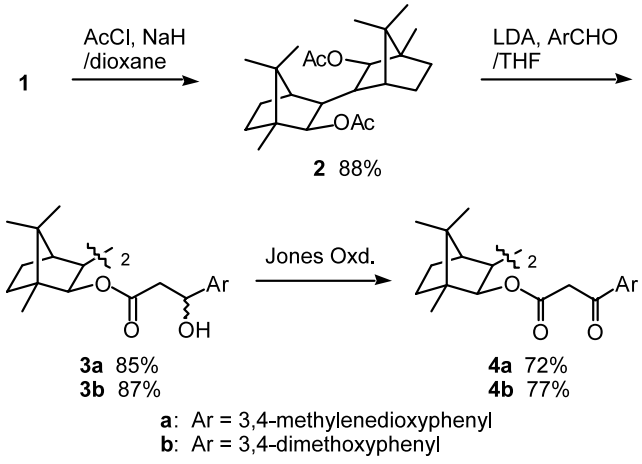
Oxidative homocoupling of aroylacetates provides useful precursors for the synthesis of furofuran lignans,[1] such as Sesamin[2] and Eudesmin.[3] Recently, we have reported the first stereoselective homocoupling of chiral aroylacetate derivatives using (4*R*,5*S*)-3,4-dimethyl-5-phenyl-2-imidazolidinone as a chiral auxiliary.[4] The stereoselectivities of the mainly formed (*R*,*R*)-dimers were, however, moderate (70–72% de). Therefore, a more efficient chiral auxiliary is desired. Herein, we report that the oxidative intramolecular coupling of diaroylacetates derived from (1*R*,1′*R*)-*exo*,*exo*′-3,3′-biisoborneol[5] as a difunctional chiral auxiliary takes place more stereoselectively.

In preliminary experiments, we found that the intermolecular coupling of chiral aroylacetates prepared from (−)-menthol, (−)-*endo*-borneol, and (−)-*exo*-borneol resulted in non-stereoselective formation of the three isomeric dimers [approximately (*R*,*R*):(*R*,*S*):(*S*,*S*) = 1:2:1]. Next, we attempted this type of oxidative coupling in the intramolecular mode. For this purpose, we selected (1*R*,1′*R*)-*exo*,*exo*′-3,3′-biisoborneol **1** as a difunctional chiral auxiliary. Since **1** was obtained in poor yields (<20%) according to the reported method[5] for oxidative coupling of (+)-camphor with $CuCl_2$, we modified the preparation of **1** as shown in Scheme 1. The oxidation of the Li-enolate of the (+)-camphor with $PhI(OAc)_2$ in THF and subsequent LAH reduction of the resulting mixture gave **1** in 54% overall yield after recrystallization (three times) from the crude products. The starting diaroylacetates of **1** were synthesized in three steps as depicted in Scheme 2: diacetylation of **1**, condensation of the diacetates **2** with aromatic aldehydes, and Jones oxidation of the resulting β-hydroxy esters **3** afforded diaroylacetates **4**.



Scheme 1.



Scheme 2.

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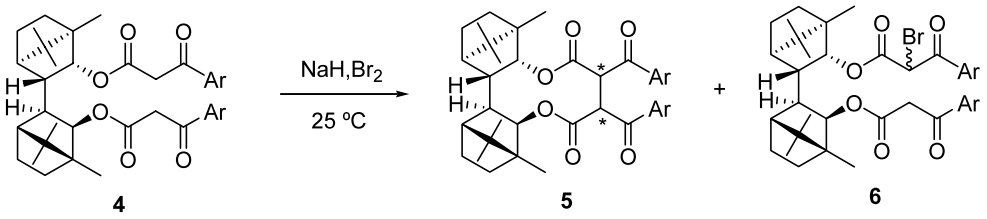
Table 1. Oxidative intramolecular coupling of **4** to **5** with NaH–Br_2

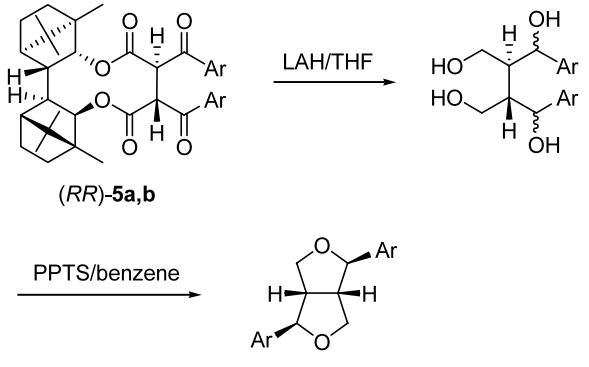


Run	4	Solvent	NaH (equiv.)	Time (h)	Yield[a] (%) of 5	(*R*,*R*):(*R*,*S*):(*S*,*S*)[b]	Yield[a] (%) of 6
1	**4a**	DMF	2.5	6	**5a** 95	29:51:20	–
2	**4a**	THF	2.5	6	Trace		**6a** 80
3	**4a**	DMF/THF (1:1)	2.5	6	**5a** 47	93:5:2	**6a** 45
4	**4a**	DMF/THF (1:1)	2	6	**5a** 59	22:53:25	**6a** 34
5	**4a**	DMF/THF (1:1)[c]	2.5	1+12	**5a** 83	96:3:1	–
6	**4b**	DMF	2.5	6	**5b** 92	32:43:25	–
7	**4b**	DMF/THF (1:1)[c]	2.5	1+12	**5b** 78	97:2:1	–

[a] Isolated yields.
[b] Determined by ^{1}H NMR spectra (see Ref. 6).
[c] THF was added after 1 h (see text).

The results of the oxidative coupling of **4a** (Ar = 3,4-methylenedioxyphenyl) by the successive treatment with NaH and Br_2 (1 equiv.) at 25°C are summarized in Table 1. The reaction with 2.5 equiv. of NaH in DMF gave the intramolecularly coupled product **5a** in excellent yield (95%), but the ratio of the three diastereomers of **5a** was essentially statistical (run 1). When the reaction was performed in THF, monobromide **6a** was obtained as the predominant product (run 2). The formation of **6a** was probably due to rapid proton abstraction from the brominated methyne group in **6a**. On the other hand, the stereoselective formation of (*R*,*R*)-**5a** [(*R*,*R*):(*R*,*S*):(*S*,*S*) = 93:5:2] resulted from the reaction in a mixed solvent of DMF/THF (1:1), although accompanied with a considerable amount of **6a** (run 3). Treatment with 2 equiv. of NaH in the same solvent, however, brought about a statistical ratio of **5a** (run 4). These results suggest the following three points: (1) The kinetic formation of **5a** is non-stereoselective; (2) the isomers of **5a** are equilibrated in the presence of an excess of NaH in DMF/THF (1:1); (3) (*R*,*R*)-**5a** is much more thermodynamically stable than the other two isomers. Indeed, isomerization from an (*R*,*R*):(*R*,*S*):(*S*,*S*) = 29:51:20 mixture of **5a** to an (*R*,*R*):(*R*,*S*):(*S*,*S*) = 95:4:1 mixture was observed by treatment with 1 equiv. of NaH in the same solvent (25°C, 6 h). On the other hand, the isomerization of **5a** could barely be detected within 6 h in DMF at 25°C and in DMF/THF (1:1) at 0°C. The reaction of **5a** with NaH in DMF at 60°C led to a complex mixture. In the previously reported intermolecular coupling of chiral 1-aroylacetyl-2-imidazolidinones,[4] such isomerizations of the coupled products were not observed. To obtain the intramolecularly coupled products in high yield and selectivity in one-pot, the reaction was initially carried out in DMF as run 1 (25°C, 1 h) and then the same amount of THF was added to the reaction mixture to attain equilibrium (25°C, 12 h, run 5). By using this procedure, (*R*,*R*)-**5a** was obtained in good yield (83%) with high stereoselectivity [(*R*,*R*):(*R*,*S*):(*S*,*S*) = 96:3:1]. Another diaroylacetate **4b** (Ar = 3,4-dimethoxyphenyl) was also transformed to (*R*,*R*)-**5b** stereoselectively according to the method of run 5 (run 7).

Fortunately, the major isomers of **5a** and **5b** could be isolated from the other isomers by column chromatography on silica gel. Their absolute stereochemistry was confirmed to be (*R*,*R*)- by a two-step conversion to (−)-Sesamin **7**[7] and (−)-Eudesmin **8**:[8] LAH reduction in THF (reflux, 6 h) and subsequent treatment with PPTS in benzene (reflux, 12 h, Scheme 3). In addition, the chiral auxiliary **1** was recovered in more than 90% yield.



Scheme 3.

The equilibriation of the three isomers of **5** was observed as described previously. Semiempirical and DFT calculations[9] were, therefore, carried out on the three isomers of dibenzoylacetate **9** (Ar = phenyl in **5**) as a model compound to evaluate the energies of their optimized structures (Fig. 1). As exhibited in Table 2,

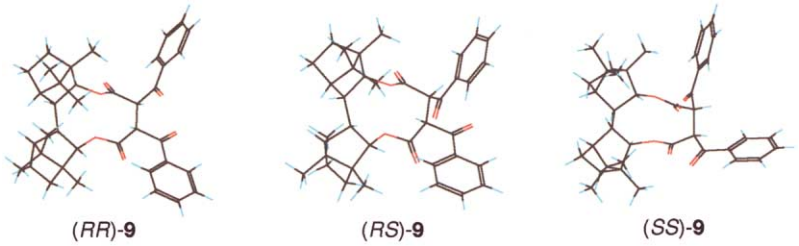


Figure 1.

Table 2. Relative energies between isomers of **9** (kcal/mol)

Method	(*R*,*R*)-**9**	(*R*,*S*)-**9**	(*S*,*S*)-**9**
RHF/AM1	0	5.13	3.84
RHF/PM3	0	3.58	3.65
RB3LYP 3-21G*	0	4.20	2.84
RB3LYP 6-31G*	0	1.32	4.16

all the methods show that (*R*,*R*)-**9** is the most thermodynamically stable isomer. These computational results are consistent with the experimental results.

In conclusion, the oxidative intramolecular coupling of the diaroylacetates of (1*R*,1′*R*)-*exo*,*exo*′-3,3′-biisobornneol with NaH–Br_2 gave the corresponding (*R*,*R*)-isomers in high stereoselectivity (92–94% de). The stereoselectivity was considerably improved by this intramolecular methodology, when compared with the intermolecular coupling previously reported by us.[4]

The typical procedure for the oxidative coupling of **4** with NaH-Br_2 is as follows (run 5 in Table 1): To a suspension of NaH (2.5 mmol) in DMF (2.5 mL) was added a solution of **4** (1.0 mmol) in DMF (2.5 mL) at 25°C under N_2. After the mixture was stirred for 30 min, Br_2 (160 mg, 1.0 mmol) was added. After the mixture was stirred for an additional hour, THF (5 mL) was added. The mixture was stirred for a further 12 h, diluted with 1 M HCl (20 mL), and then extracted with Et_2O. The major isomer of **5** was isolated by column chromatography on silica gel (hexane/ethyl acetate), and gave satisfactory spectroscopic data and elemental analysis. (*R*,*R*)-**5a**: $[\alpha]_D^{25}=+110$ (*c* 0.97, $CHCl_3$). (*R*,*R*)-**5b**: mp 123–125°C; $[\alpha]_D^{25}=+100$ (*c* 0.99, $CHCl_3$).

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6. The chemical shifts (δ) of newly formed methyne protons in **5** were as follows: (*R*,*R*)-**5a** 5.03 (s); (*R*,*S*)-**5a** 4.75 and 4.79 (d, $J=3.2$ Hz); (*S*,*S*)-**5a** 5.60 (s); (*R*,*R*)-**5b** 5.13 (s); (*R*,*S*)-**5b** 4.85 and 4.89 (d, $J=3.2$ Hz); (*S*,*S*)-**5b** 5.66 (s).
7. (−)-Sesamin **7**: $[\alpha]_D^{25}=-64.0$ (*c* 1.0, $CHCl_3$), lit.[2a] $[\alpha]_D^{22}=-64.5$ (*c* 1.05, $CHCl_3$).
8. (−)-Eudesmin **8**: $[\alpha]_D^{25}=-64.7$ (*c* 1.0, $CHCl_3$), lit.[3b] $[\alpha]_D^{23}=-64.2$ (*c* 1.1, $CHCl_3$).
9. The calculations were carried out using the Gaussian 98W program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J. Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98W*, Revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.