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Synthesis and applications of (1*R*,5*S*,6*S*)-6-(2,2-dimethylpropanamido)spiro[4.4]nonan-1-ol as a chiral auxiliary in Diels–Alder reactions

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Abstract

A short asymmetric synthesis of (1*R*,5*S*,6*S*)-6-(2,2-dimethylpropanamido)spiro[4.4]nonan-1-ol **7** is described along with its application as a chiral auxiliary in various Diels–Alder reactions. The enantioselectivity of the Diels–Alder adducts ranged from 86–98% ee. The Diels–Alder adducts were easily removed from the chiral auxiliary and the latter was recyclized. The absolute and relative stereochemistry of **7** was determined from an X-ray crystal structure of the *p*-bromobenzoate derivative of **7**.

1. Introduction

In 1996 we reported[2] that the mono-pivalate mono-acrylate diester of (+)-(1*S*,5*S*,6*S*)-spiro[4.4]-nonane-1,6-diol **1**[3–5] underwent a Diels–Alder reaction with cyclopentadiene to produce the expected *endo*-bicyclo adduct **2** in >97% de (Scheme 1). Subsequent cleavage of the resulting adduct by iodolactonization yielded iodolactone **3** in 70% yield with an ee of >97% and spiro-alcohol **4** which could be reused. The major drawback of this procedure was that adduct **2** is a diester and it was difficult to selectively hydrolyze the bicycloester in the presence of the pivalate. Iodolactonization[6] was the only method that allowed the selective removal of the bicyclo adduct from the chiral auxiliary leaving the pivalate group intact (i.e. **4**). We rationalized that if the pivalate in **1** was changed to pivalamide **5**, then the selective hydrolysis of the ester in adduct **6** would be straightforward. In addition, not many 1,3-aminoalcohols have been reported as chiral auxiliaries.[7] We herein report the asymmetric synthesis of (1*R*,5*S*,6*S*)-6-(2,2-dimethylpropanamido)spiro[4.4]nonane-1-ol **7** and its application as a chiral auxiliary in a variety of Diels–Alder reactions.

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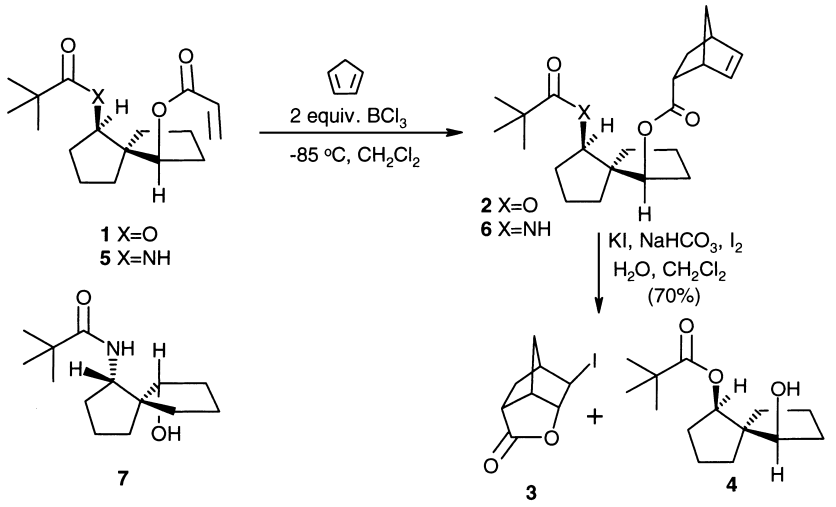
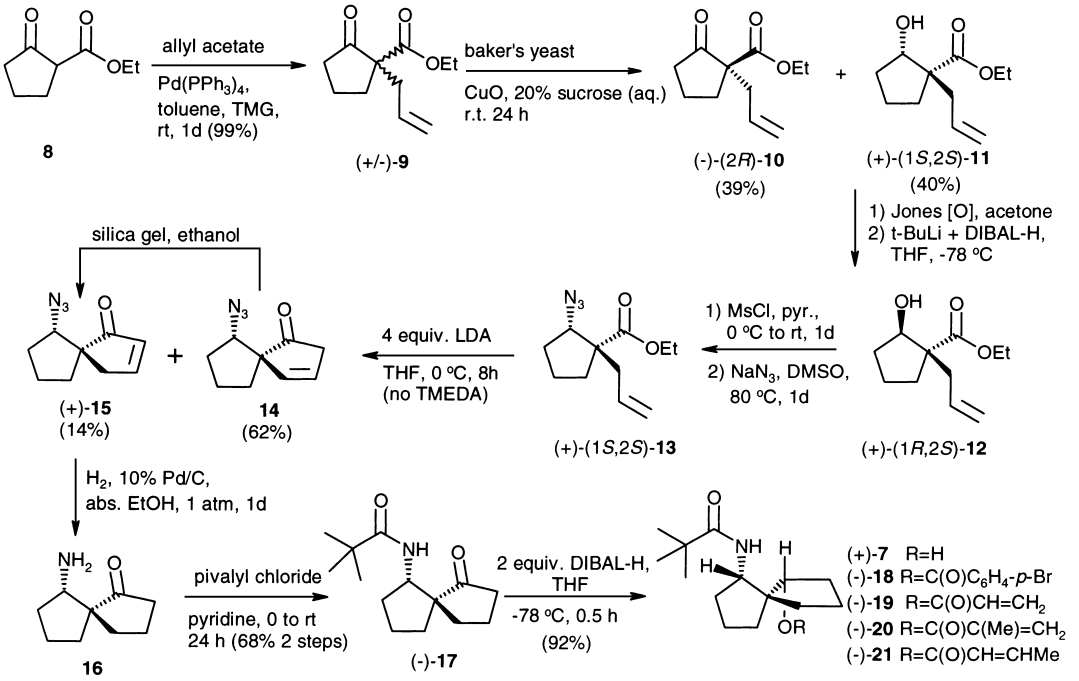


Scheme 1.

2. Results and discussion

Compound (+)-**7** was prepared as shown in Scheme 2. The allylation of 2-ethoxycarbonyl-1-cyclopentanone **8** has been reported using various bases and allyl bromide in moderate to high yields.[8] However, work on asymmetric allylations of β-ketoesters by Trost[9] revealed that almost



Scheme 2.

quantitative yields can be obtained when palladium-catalyzed reaction conditions are used. Although **9** was desired in enantiopure form, allylation of **9** via Trost's method gave poor ee's,[10] so we decided to make **9** as a racemate. Ester **9** was formed in quantitative yield using $Pd(PPh_3)_4$ (0.4 mol%) and allyl acetate (1.2 equiv.). Baker's yeast reduction of (±)-**9** with CuO gave a mixture of (–)-(2*R*)-**10** (39%, $[\alpha]_D^{20}$ –37.8 (*c* 1.20, $CHCl_3$)) and (+)-(1*S*,2*S*)-**11** (40%, $[\alpha]_D^{20}$ +27.9 (*c* 1.20, $CHCl_3$)).[11] Unfortunately, baker's yeast reduction of the ketone functionality in (±)-**10** provided the incorrect stereochemistry at the alcohol in (+)-**11** for the synthesis of (+)-**8**.[12] Therefore, the alcohol in (+)-**11** was oxidized to ketone (+)-**10** with Jones' reagent and subsequently reduced with lithium *t*-butyldiisobutylaluminium hydride[2] (1.1 equiv.) to provide exclusively (+)-**12** ($[\alpha]_D^{20}$ +19.1 (*c* 1.21, $CHCl_3$)) in yields ranging from 72–94%. Conversion of the alcohol in (+)-**12** to the mesylate (2 equiv. MsCl and pyridine, 99%) followed by the treatment with 4 equiv. sodium azide[13] (DMSO) gave (+)-**13** (62–76%, $[\alpha]_D^{24}$ +43.2 (*c* 1.25, $CHCl_3$)). Treatment of (+)-**13** according to the procedure reported by Thebtaranonth et al.[14] with LDA (4 equiv., no TMEDA) at 0°C provided a 72:18 mixture of **14**:(+)-**15**. Stirring the mixture in ethanol containing silica gel overnight afforded only (+)-**15** ($[\alpha]_D^{18}$ +47.8 (*c* 1.15, $CHCl_3$)), which was purified on a silica gel column (76% yield). Catalytic hydrogenation of (+)-**15** gave **16** in which both the double bond and the azide were reduced. Ketone **16** was found to be unstable and was treated immediately with pivalyl chloride (2 equiv.) in pyridine to afford pivalamide (–)-**17** (68%, two steps, $[\alpha]_D^{20}$ –73.2 (*c* 1.21, $CHCl_3$)). We initially thought that the pivalamide would block the top face of the ketone such that reduction would occur from behind ketone (–)-**17** to afford the *cis*,*cis*-relationship between the amide and the resulting alcohol. However, treatment of (–)-**17** with a variety of reducing agents provided the *cis*,*trans*-isomer (+)-**7** in 92% yield. The *cis*,*trans*-relationship and the absolute stereochemistry of (+)-**7** was proven by obtaining an X-ray crystal structure on the *p*-bromobenzoate (–)-**18** (Fig. 1).[15] Finally, three Diels–Alder precursors (–)-**19** (68–82% yield), (–)-**20** (79% yield) and (–)-**21** (69–78% yield after migration)[16] were prepared by treatment of (+)-**7** with acryloyl chloride, methacryloyl chloride and *trans*-crotonyl chloride respectively (Et_3N, CH_2Cl_2).

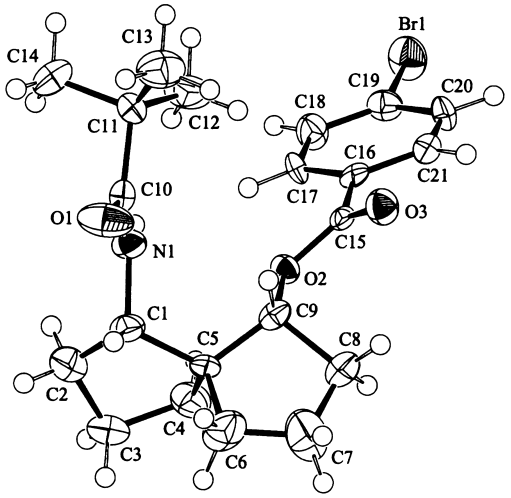


Figure 1. ORTEP of *p*-bromobenzoate **18**

The results from the Diels–Alder reactions of (–)-**19**, (–)-**20** and (–)-**21** with a variety of dienes are summarized in Table 1. All reactions were performed using 2 equiv. of BCl_3 at –78°C for 8 h and gave adducts in yield ranging from 74–82%. Reaction of (–)-**19** with cyclopentadiene and cyclohexadiene afforded only *endo* adducts and examination of the ^1H NMR spectra indicated that only one *endo* isomer was formed. Cleavage of the adduct from the auxiliary (NaOH, MeOH, reflux 1 day) provided (+)-**22** and (+)-**23** with % ee's >98% (by optical rotation measurements) along with alcohol (+)-**7**, which was easily separated (silica gel chromatography) and recycled. The reaction of (–)-**19** with furan gave a 2:1 ratio of *endo*:*exo* adducts (by ^1H NMR integration) having a % de of 79 and 78%, respectively (by ^1H NMR integration). Unfortunately, the adducts could not be separated either before or after cleavage from the chiral auxiliary (NaOH, MeOH, reflux). The Diels–Alder reaction of (–)-**7** with isoprene gave a mixture of diastereomers that were hydrolyzed immediately in refluxing NaOH in MeOH to provide compound (+)-**25** with a 92% ee. When methacrylate (–)-**20** was used as the dienophile component in the Diels–Alder reaction with cyclopentadiene, only the *endo* isomer was formed but in a disappointing 21% de and further experiments were not carried out on this system. Lower

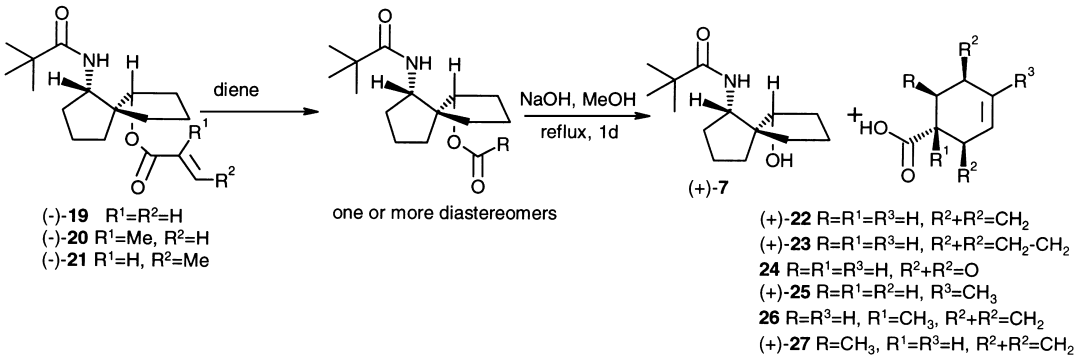
Table 1
Diels–Alder results with (–)-**19**, (–)-**20** and (–)-**21**[a]

						Product	
SM	**Diene**	**Yield**	***Endo*:*Exo* Ratio**	**de[b] *Endo***	**de[b] *Exo***	**Product (ee[c])**	**Absolute Config.[d]**
(-)-**19**		70%	100:0	>98%	-	(+)-**22** (>98%)	*R*[17]
(-)-**19**		82%	100:0	>98%	-	(+)-**23** (>98%)	*R*[18]
(-)-**19**		74%	2:1	79%	78%	**24** (-)[f]	-
(-)-**19**		79%	na[e]	na[e]	na[e]	(+)-**25** (92%)	*R*[19]
(-)-**20**		72%	100:0	21%	-	**26**(-)[g]	-
(-)-**21**		81%	8:1	86%	64%	(+)-**27** (86%)[h]	*R*[20]

a) All reactions performed in CH_2Cl_2 at -78 °C for 8 h using 2 equiv. BCl_3. b) Measured by integration of the ^1H NMR spectrum. c) Measured by comparing the specific rotation of the product to the reported specific rotation. d) Assigned by comparison of the sign of the optical rotation of the mixture to that reported in the literature for the pure enantiomer. e) Not applicable. f) The *endo* and *exo* isomers could not be separated by silica gel chromatography, so the optical rotation could not be measured. g) The chiral auxiliary was not removed as the % de was low. h) *Endo* isomer only.

diastereoselectivity was observed for precursor (–)-**21** with cyclopentadiene; an 8:1 ratio of *endo*:*exo* isomers was formed with 86 and 64% de's, respectively (by ^1H NMR). Acid (+)-**27** was formed with an 86% ee after it was removed from the chiral auxiliary (NaOH, MeOH).

In summary, we have developed a short synthesis of spiroaminoalcohol (+)-**7** and shown it to be a useful chiral auxiliary for Diels–Alder reactions with a variety of dienophiles and dienes. The presence of the pivalamide allows for the selective cleavage of the Diels–Alder adducts to provide optically active acids and alcohol (+)-**7**, which can easily be separated and recycled. Further uses of spiroaminoalcohol (+)-**7** are currently underway including solid-phase applications.



3. General experimental procedures

3.1. General procedure for Diels–Alder reactions

The starting dienophile (–)-**19**, (–)-**20**, or (–)-**21** (0.34 mmol) was placed in a dry 25 mL flask under N_2 containing crushed and flame dried 4 Å molecular sieves (100 mg) in dry CH_2Cl_2 (7 mL). The mixture was cooled to –78°C and BCl_3 (0.68 mmol of 1 M solution in CH_2Cl_2) was added. The mixture was stirred at –78°C for 0.5 h at which point the dienophile (5 equiv. freshly distilled or cracked and collected at –78°C) was added. The mixture was stirred at –78°C for 8 h and then passed through a plug of silica gel packed in CH_2Cl_2. The silica gel was rinsed with Et_2O and the solvents combined and removed in vacuo. The residue was purified by silica gel chromatography (4:1 hexanes:EtOAc) to give the purified product(s).

3.2. General procedure for the removal of the Diels–Alder adduct from the chiral auxiliary

The purified Diels Alder adduct from the reaction of (–)-**19** with cyclopentadiene (0.12 mmol) was placed in a 25 mL round bottomed flask containing a condenser. NaOH (10 mL of 5N) and MeOH (2 mL) was added and the mixture refluxed at 110°C for 1 day. The mixture was cooled to rt and the MeOH removed in vacuo. H_2SO_4 (15%) was added at 0°C until the pH of the solution was 2–3. The mixture was extracted with EtOAc (3×25 mL), dried (Na_2SO_4) and the solvent removed to leave a mixture of the chiral auxiliary (+)-**7** and adduct (+)-**22**. The mixture was separated on a silica gel column (4:1 hexanes:EtOAc) to give 79% yield of (+)-**22** (0.09 mmol) and a 73% yield of recovered auxiliary (+)-**7** (0.09 mmol).

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12. Compound (–)-(2*R*)-**10** can also be used to synthesize the antipode (–)-**7**. Reduction of (–)-(2*R*)-**10** with *t*-butyldiisobutylaluminium hydride provides (–)-(1*S*,2*R*)-**12**.
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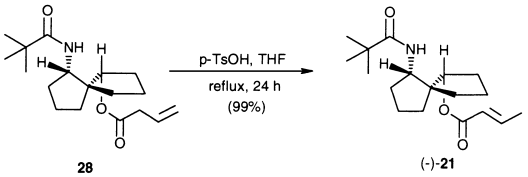
15. Compound (–)-**18**: monoclinic $P2_1$ (#4); a = 8.979(2) Å, b = 10.228(4) Å, c = 10.910(3) Å, $\beta = 93.02(2)^{\circ}$, $V = 1000.6(5)$ Å^3; $Z = 2$; $R = 0.044$; $R_w = 0.091$; Flack parameter = –0.01(2). Bijvoet analysis was performed. A refinement of the inverted structure was carried out which converged with $R = 0.069$, $R_w = 0.157$ and the Flack parameter = 1.01(2) and was therefore rejected as the absolute configuration present in the crystal.
16. Interestingly, the initial product from the reaction of (+)-**7** with *trans*-crotonyl chloride was ester **28** with a unconjugated double bond. Treatment of ester **28** with cat. *p*-TsOH in THF at reflux for 24 h provided (–)-**21** in quantitative yield.



28 (-)-**21**

17. Compound (+)-**22**: $[\alpha]_D^{22}$ +69.2 (*c* 0.48, $CHCl_3$). Literature: $[\alpha]_D^{20}$ –68.7 (*c* 0.53, $CHCl_3$): Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015.
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20. Compound (+)-**27**: $[\alpha]_D^{21.6}$ +115.9 (*c* 0.345, $CHCl_3$). Literature: $[\alpha]_D$ +134 (*c* 0.7, $CHCl_3$): Kouklovsky, C.; Pouihès, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672.