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Asymmetric Cyclopentannelation. Chiral Auxiliary on the Allene

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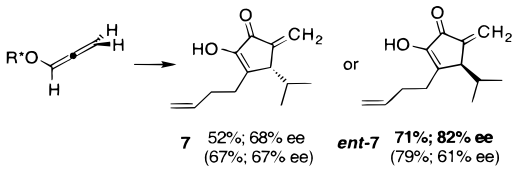
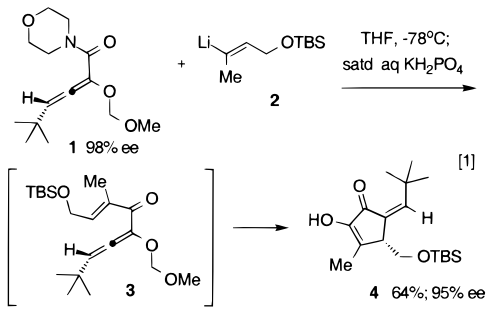
ABSTRACT



An enantioselective variant of the synthesis of cross-conjugated cyclopentenones, based on D-glucose-derived chiral auxiliaries, is described. Minor modification of the method makes it applicable to the preparation of both enantiomeric series of products. Both enantiomers of the key intermediate in our roseophilin synthesis have been prepared.

We recently published an asymmetric variant of the allene ether Nazarov reaction, in which axial chirality of the allene component was transferred to the tetrahedral ring carbon of the product (eq 1).[1] For example, (*R*)-allene **1** was treated



with vinyllithium **2** in THF at −78 °C. Spontaneous Nazarov cyclization during acidic workup of the reaction led to cross-conjugated (*Z*)-cyclopentenone **4** with >95% chirality transfer. We have interpreted this result as being the consequence of a steric bias that strongly favors one of the two allowed modes for conrotatory ring closure of the putative intermediate **3**, the one in which the *tert*-butyl group rotates away from the silyloxymethyl group. This hypothesis is supported by the observed strong kinetic preference for the *Z* exocyclic double bond geometry in all cyclopentenone products.[2] The method of eq 1 requires a stereogenic allene; therefore the allene must be γ-substituted. The γ-substituent of the allene appears on the exocyclic double bond of the cyclopentenone product. Our goal was to develop an enantioselective synthesis of cyclopentenones with an unsubstituted exocyclic double bond by means of a chiral auxiliary on the allene.

Carbohydrates and their derivatives are commonly used as chiral auxiliaries;[3] therefore we decided to examine a simple auxiliary that could be derived from D-glucose. The choice of auxiliary was made without the guidance of any mechanistic hypothesis. α-D-Glucose was combined with propargyl alcohol to provide a mixture of anomeric propargyl glucosides (2:1).[4] The mixture was permethylated (68%

(1) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895−9896.

(2) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

(3) This area has been reviewed: (a) Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336−358. (b) Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 288−290. See also: (a) Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197−1207. (b) Chika, J-i.; Takei, H. *Tetrahedron Lett.* **1998**, *39*, 605−608. (c) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183−4184. (d) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536−8543. (e) Chiappe, C.; Moro, G. L.; Munforte, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2311−2317. (f) Rochet, P.; Vatèle, J.-M.; Goré, J. *Synlett* **1993**, 105−107. (g) Yoshida, T.; Chika, J-i.; Takei, H. *Tetrahedron Lett.* **1998**, *39*, 4305−4308.

(4) Bollenback, G. N. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfram, M. L., Eds.; Academic Press: New York, 1963; Vol. 2, pp 326−328.

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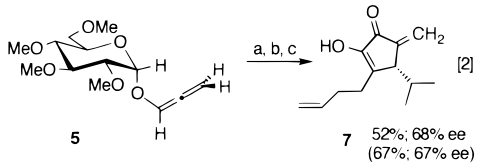
overall yield) by exposure to powdered potassium hydroxide, iodomethane, and catalytic 18-crown-6 in THF.[5] The 2:1 mixture of α and β anomers was separated, and the individual diastereomers were isomerized to the corresponding allenes **5** and **29** by treatment with potassium *tert*-butoxide at 60 °C for 1 h.[6]

Equation 2 summarizes the first cyclization reaction, which we performed with the α anomer of the asymmetric allene

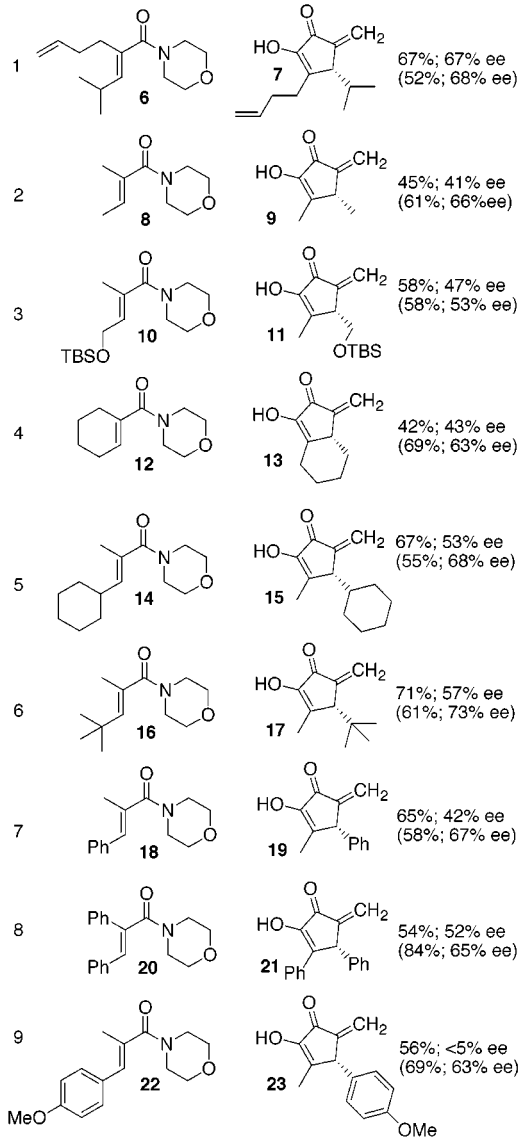


(a) *n*-BuLi, LiCl, THF, -78°C; (b) -78°C, 1 h, **6**; (c) HCl, HFIP, 0°C (or HCl, EtOH, -78°C).

reagent. α-Deprotonation of the allene ether took place with *n*-butyllithium in THF; however, the resulting allenyllithium species was quite unreactive compared to 1-lithio-1-(methoxy)methoxyallene. Addition of 4 equiv of LiCl[7] to the solution of the anion improved the nucleophilicity so that addition to morpholino amide **6** took place.[8] Cyclization was induced by transferring the reaction mixture to a solution of HCl in ethanol at −78 °C. The solution was warmed to room temperature, worked up, and chromatographed to provide cyclopentenone **7** in 67% yield with 67% ee.[9] Cyclopentenone **7** is a key intermediate in our roseophilin synthesis.[10]

A series of amides was examined to determine the scope of the method.[11] Table 1 summarizes our results.[12] Product

Table 1



yields varied between 42% and 71%, whereas enantiomeric excesses varied between 41% and 67%, with no clear trends in evidence. In one case (entry 9) racemic product was obtained (vide infra). The absolute stereochemistry of **11** was

(5) Bessodes, M.; Shamsazar, J.; Antonakis, K. *Synthesis* **1988**, 560−562.

(6) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916−924.

(7) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

(8) Martin, R.; Romea, P.; Tey, C.; Urpi, F.; Vilarrasa, J. *Synlett* **1997**, 1414−1416.

(9) The enantioselectivities were determined by HPLC on a Daicel Chiralcel OD (250 mm × 10 mm) chiral column with mixtures of 2-propanol and hexanes as eluant, with a flow rate of 1 mL/min with UV detection at 254 nm; co-injection with racemate confirmed the peak assignment in the chromatogram.

(10) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649−651.

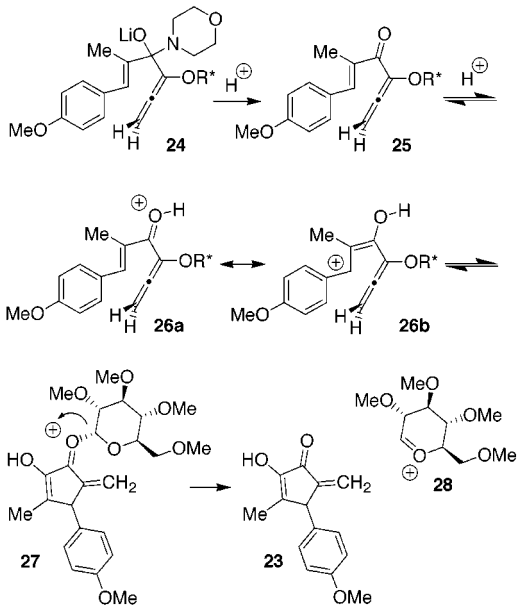
(11) Amides **10**, **14**, and **16** were prepared by Horner-Emmons condensation of the corresponding aldehydes with triethyl 2-phosphonopropionate followed by conversion to the amide; see: Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171−4174. Amides **8**, **12**, **18**. and **20** were prepared from the corresponding commercially available acids via the acid chlorides.

(12) **Typical Procedure (entry 1, EtOH quench).** To a solution of LiCl (63 mg, 1.5 mmol) and allene **5** (100 mg, 0.365 mmol) in 1.5 mL of THF at −78 °C was added *n*-BuLi (160 μL, 2.28 M in hexanes, 0.365 mmol). After 30 min, a solution of amide **6** (38 mg, 0.16 mmol) in 1.5 mL of THF was added at −78 °C via cannula. After 1 h the reaction mixture was quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in 3 mL of EtOH at −78 °C. The flask was removed from the cooling bath and diluted with pH 7 buffer, brine, and EtOAc. The aqueous phase was extracted with EtOAc (3×), and the combined aqueous extracts were washed with brine and dried ($MgSO_4$). Purification by flash column chromatography on silica (5% EtOAc in hexanes) gave cyclopentenone **7** (22 mg, 67% yield, 67% ee) as a colorless oil: R_f = 0.35 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (br s, 1H), 6.10 (s, 1H), 5.83 (ddt, J = 17.1, 10.5, 6.1 Hz, 1H), 5.41 (s, 1H), 5.07 (dd, J = 17.1, 1.5 Hz, 1H), 4.99 (br d, J = 10.5 Hz, 1H), 3.20 (br s, 1H), 2.77 (m, 1H), 2.45−2.22 (m, 3H), 2.15 (sept d, J = 7.1, 2.9 Hz, 1H), 1.10 (d, J = 7.1 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 151.1, 144.4, 141.7, 137.4, 116.7, 115.3, 47.1, 30.7, 29.1, 25.9, 21.7, 16.3; IR (neat) 3310 (br), 2965, 1680, 1625, 1395, 1095, 915, 820 cm^{-1}; MS m/z 206 (M^+, 35), 164 (79), 163 (100), 135 (65), 123 (91), 122 (43), 117 (36); exact mass calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1283; chiral HPLC (2.5% 2-propanol in hexanes) t_R = 23.7 min (major), t_R = 25.3 min (minor); $[\alpha]^{27}_D$ +5° (c 0.0080, $CHCl_3$). **Typical Procedure (entry 1, HFIP quench).** To a solution of LiCl (83 mg, 2.0 mmol) and allene **5** (155 mg, 0.565 mmol) in 3 mL of THF at −78 °C was added *n*-BuLi (245 μL, 2.44 M in hexanes, 0.598 mmol). After 30 min, a solution of amide **6** (71 mg, 0.30 mmol) in 3 mL of THF at −78 °C was added via cannula. After 1 h, the reaction mixture was quenched by rapid addition through a large bore cannula to HCl (generated by addition of 750 μL of acetyl chloride) in 6 mL of HFIP at 0 °C. The flask was removed from the cooling bath and diluted with pH 7 buffer, brine, and EtOAc. The aqueous phase was extracted with EtOAc (3×), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash column chromatography on silica (5% EtOAc in hexanes) gave cyclopentenone **7** (32 mg, 52% yield, 68% ee) as a colorless oil.

determined through chemical correlation with **4**, whose absolute stereostructure we determined crystallographically. Details of this work can be found in the Supporting Information. The absolute stereochemistry of the other entries of Table 1 was assumed to be the same as shown for **11**. The difference in ee between **19** and **23** (entries 7 and 9) was unexpected and puzzling. The reaction leading to **23** was repeated several times to make sure that the low ee was not an artifact; however, both the yield and the ee were reproducible. Consideration of the details of the mechanism allowed us to rationalize the stark difference in the reactions of **18** and **22** and also suggested the remedy that improved the enantioselectivity of the cyclization.

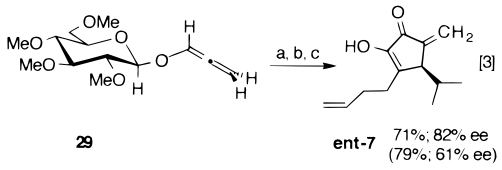
The only difference between **18** and **22** is the *p*-methoxy group in **22**; therefore it is likely that the difference in enantioselectivity for the two reactions is due to the greater stability and longer lifetime of the *acyclic* cationic intermediate **26** (Scheme 1). Addition of the anion derived from **5** to

Scheme 1



morpholino amide **22** leads to tetrahedral intermediate **24**. The diastereoselectivity for this reaction is immaterial, since proton transfer during the quench with acid leads irreversibly to ketone **25**. Proton transfer to **25**, which leads to the key intermediate **26**, is probably reversible. The stereodetermining step is the Nazarov cyclization of cation **26** to **27**. Irreversible fragmentation of **27** gives **23** and the glucose-derived cation **28**. The large increase in stability of **26**, which is conferred by the *p*-methoxy group, likely renders the ring-closure step readily reversible in this case. A longer lifetime for cation **26** provides an opportunity for loss of stereochemical integrity of the trisubstituted alkene (see **26a**) and hence will lead to racemic product. If one assumes that the chiral auxiliary imposes a preference for one of the two possible conrotations of pentadienyl cation **26b**, then the geometrical isomers of the trisubstituted alkene will lead to enantiomeric products. It occurred to us that one way to mitigate the problem would be to increase the rate of the irreversible cleavage of cation **27**. This could be expected to have a beneficial effect on the reaction yield, as well as the enantioselectivity, since **26** and **27** may undergo undesired reactions that erode the yield of **23**. We postulated that cleavage of **28** would be faster at temperatures higher than −78 °C and in a solvent better able to stabilize carbocations than ethanol. For this approach to be successful, the solvent must exert a greater stabilizing effect on **28** (and the transition state leading to **28**) than **26**. Accordingly, the cyclization leading to **23** was performed in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[13] The yield for the cyclization to **23** improved modestly in this solvent, to 69% (Table 1, entry 9), but the ee was now 63%. A comparison of the cyclizations in ethanol vs HFIP reveals that the ee of the products from the HFIP reaction is better than in ethanol in all cases except for **7**. The ee for **7** may have been optimal even in ethanol. For the cyclizations in HFIP a trend can be discerned. The products derived from amides bearing a large group at the β-carbon atom (viz. *tert*-butyl, entry 6) have the highest ee's.

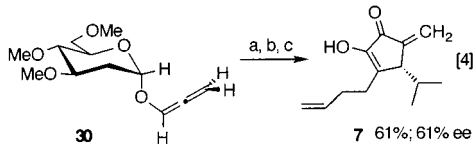
We were interested in the reactions of the β-anomeric allene, so the reaction of amide **6** with the anion derived from **29** was examined (eq 3). The yield of this reaction was



(a) *n*-BuLi, LiCl, THF, -78°C; (b) -78°C, 1 h, **6**; warm to -40°C, 1 h; cool to -78°C; (c) HCl, HFIP, 0°C (or HCl, EtOH, -78°C).

79% in ethanol and 71% in HFIP, whereas ee's were 61% and 82%, respectively. Significantly, **29** leads to the enantiomer of **7**. The reaction of **29** was also examined with amide **18**, and in this case again the enantiomer of **19** was the major product. The yield of ***ent*-19** was 81% in ethanol and 78% in HFIP, whereas ee's were 70% and 84%, respectively. On the basis of these experiments, it appears that the reactions of **29** are more enantioselective than those of **5**. It is also worth noting that the allenyl anion derived from **29** appeared to be less reactive than the anion derived from **5**. Optimal yields for the addition to morpholino amides required warming the reaction mixture to −40 °C, then cooling again to −78 °C prior to quenching.[14]

A single reaction was conducted with allene **30** (eq 4), which was derived from 2-deoxy-D-glucose. The reaction of **30** with amide **6** is virtually indistinguishable from that of



(a) *n*-BuLi, LiCl, THF, -78°C; (b) -78°C, 1 h, **6**; (c) HCl, EtOH, -78°C.

5, which leads to the conclusion that the C2 methoxyl group in **5** does not influence the stereochemical outcome of the reaction.

In conclusion, a method has been described which extends the utility of the cationic cyclopentannelation reaction of allenyl ethers by providing access to both enantiomeric series of cross-conjugated cyclopentenones. Loss of the chiral auxiliary takes place during the course of the cyclization; therefore no separate cleavage step is required. The synthesis of both enantiomers of **7** constitutes an enantioselective formal total synthesis of roseophilin and of its enantiomer. The optical purity of the products appears to be greater from the reactions of **29** than from **5**. Although it is premature to speculate about the origin of the enantioselectivity, the results that have been described suggest several avenues of inquiry in the quest for improved chiral auxiliaries for the allene.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support and Dr. Huaping Hu for a sample of racemic **4**.

Supporting Information Available: IR, ^{1}H and ^{13}C NMR, and mass spectra and HPLC chromatograms for **7** and ***ent*-7**. Determination of the absolute stereochemistry of **11**. Full characterization and experimental procedures for the preparation of **5** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927−929.

(14) **Typical Procedure (HFIP quench).** To a solution of LiCl (87 mg, 2.1 mmol) and allene **29** (150 mg, 0.547 mmol) in 3 mL of THF at −78 °C was added *n*-BuLi (235 μL, 2.44 M in hexanes, 0.573 mmol). After 30 min, a solution of amide **6** (73 mg, 0.31 mmol) in 3 mL of THF at −78 °C was added via cannula. After 1 h at −78 °C, the reaction mixture was warmed from −78 to −40 °C over 1 h, cooled to −78 °C, and quenched by rapid addition through a large bore cannula to HCl in HFIP (generated by addition of 750 μL of acetyl chloride to 6 mL of HFIP) at 0 °C. The flask was removed from the cooling bath and diluted with pH 7 buffer, brine, and EtOAc. The aqueous phase was extracted with EtOAc (3×), and the combined organic extracts were washed with brine and dried over $MgSO_4$. Purification by flash column chromatography on silica (5% EtOAc in hexanes) gave cyclopentenone ***ent*-7** (45 mg, 71% yield, 82% ee) as a colorless oil: chiral HPLC (2.5% 2-propanol in hexanes) t_R = 23.7 min (minor), t_R = 25.3 min (major); $[\alpha]^{27}_D$ −7° (*c* 0.013, $CHCl_3$).