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One-Carbon Bridge Stereocontrol in Robinson Annulations Leading to Bicyclo[3.3.1]nonanes

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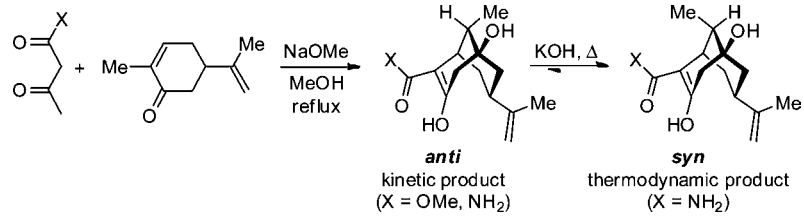
ABSTRACT



The one-carbon bridge stereochemistry of bicyclo[3.3.1]nonane products formed in the Robinson annulation reactions of 2-substituted cyclohex-2-enones was investigated. In contrast to previous reports, it was found that the major diastereomer formed places the one-carbon bridge substituent *anti* to the *β*-keto ester/amide unit introduced in the Robinson annulation. This stereoselectivity appears to be kinetically controlled. In the case of a *β*-keto amide product derived from carvone, it was demonstrated, through base-catalyzed epimerization, that thermodynamic control favors the *syn* isomer.

The framework of bicyclo[3.3.1]nonane is quite common in biologically active natural products,[1] and many synthetic and biosynthetic pathways involve formation and transformation of this framework.[2] Due to the importance of this structural feature, a number of efficient and highly stereoselective synthetic methods have been established.[3] However, introduction of a stereocenter at the one-carbon bridge has rarely been reported and remains an unsolved problem.

Interest in ring system **1**, present in the natural product vinigrol,[4] prompted us to investigate the two-carbon ring expansion of the tricyclic precursor **2**, which we envisioned could be prepared from appropriately substituted bicyclo[3.3.1]nonane **3a** (Scheme 1). Thus we explored the Robinson annulation depicted schematically in structure **4** as a route to bicyclo[3.3.1]nonane **3a** paying special attention to the stereochemistry of the allyl group attached to the one-carbon bridge. Herein we report the results of this exploration.

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(4) For the isolation and biological activities of vinigrol, see: (a) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292. (b) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 25. (c) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31.

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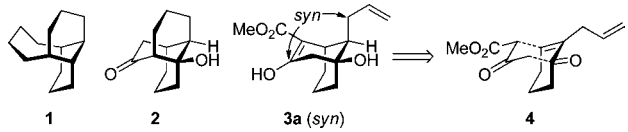
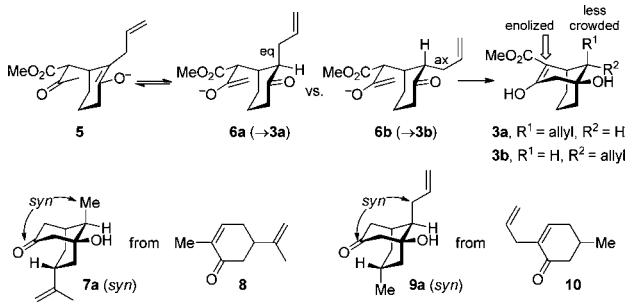
Scheme 1. Stereoselective Robinson Annulation Reaction Required To Develop a Ring-Expansion Approach to Vinigrol



Stereochemistry at the one-carbon bridge will be governed by the competition of aldol ring-closure reactions of diastereomeric intermediates **6a** and **6b** formed from Michael adduct **5** (Scheme 2). There are several lines of

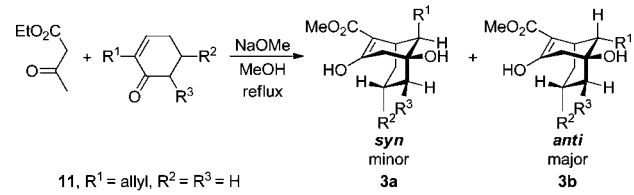
Scheme 2. Stereochemistry at the One-Carbon Bridge Is Governed by the Competing Aldol Reactions **6a** → **3a** and **6b** → **3b**



reasoning that might lead one to expect that the aldol ring closure of **6a**, leading to the desired stereochemistry present in **3a**, might be the favored pathway. First, the reactive conformer of **6a** (equatorial allyl) should be lower in energy than **6b** (axial allyl). Second, Robinson annulation product **3a** (derived from **6a**) is lower in energy than its epimer **3b** (derived from **6b**) as a result of the enolization of the β-keto ester, which removes a 1,3-diaxial involving the allyl group. Indeed, two similar Robinson annulations previously reported provide precedent for the major product possessing the desired stereochemistry **3a**. Theobald reported that **7a** is the major product formed by annulation of carvone (**8**) with ethyl acetoacetate, followed by saponification and decarboxylation.[5] Kraus reported that **9a** was the major product (>20:1 diastereoselectivity) formed from the analogous annulation/decarboxylation sequence utilizing 2-allyl-5-methyl-2-cyclohexenone (**10**).[6]

To our surprise, the Robinson annulation reaction of ethyl acetoacetate with 2-allyl-2-cyclohexenone (**11**) gave **3b** (*anti*) rather than **3a** (*syn*) as the major product (Table 1, entry 1). Repeating the Robinson annulation originally reported by Kraus, we were also surprised to find that **12b** (*anti*) was the major diastereomer obtained in the reaction of ethyl acetoacetate with 2-allyl-5-methyl-2-cyclohexenone, **10** (entry 2). In order to directly compare our selectivity to the Kraus result, the **12b**/**12a** mixture was decarboxylated to produce a **9b**/**9a** mixture with the same diastereomer ratio

Table 1. Stereochemical Outcome of Robinson Annulation Reactions Leading to Bicyclo[3.3.1]nonanes



11, R^1 = allyl, R^2 = R^3 = H	**3a**	**3b**
10, R^1 = allyl, R^2 = Me, R^3 = H	**12a**	**12b**
13, R^1 = allyl, R^2 = H, R^3 = Me	**14a**	**14b**
15, R^1 = $(CH_2)_3OH$, R^2 = R^3 = H	**16a**	**16b**
8, R^1 = Me, R^2 = MeC=CH_2, R^3 = H	**17a**	**17b**

entry	starting material	ratio (*syn*/*anti*)[a]	total yield (%)
1	**11**[b]	1:4.3	54
2	**10**[c]	1:3.5	42
3	**13**[d]	1:4.9	31
4	**15**[e]	1:5	43
5	**8**[f]	1:4	56

[a] The ratio is based upon the ^{1}H NMR of the crude product. [b] The compound is prepared according to the literature.[7] [c] The compound is prepared according to the literature.[8] [d] The compound is prepared by methylation of compound **11**.[9] [e] The compound is prepared by hydroboration−oxidation of compound **11** using Cy_2BH·THF according to a known procedure.[10] [f] Carvone (**8**) is commercially available.

and **9b** (*anti*) rather than **9a** (*syn*) as the major product. Compound **14b** (*anti*) was the major diastereomer obtained in the reaction of ethyl acetoacetate with 2-allyl-6-methyl-2-cyclohexenone, **13** (entry 3). Neither the substituent on the cyclohexane ring (entries 1−3) nor the substituent at the one-carbon bridge (entries 4 and 5) significantly influence stereoselectivity. In the reaction of ethyl acetoacetate with **15** (3-hydroxypropyl is the substituent at the one-carbon bridge) and carvone (**8**), the *anti* diastereomers **16b** and **17b** are the major products formed. The configuration of the one-carbon bridge center has been unambiguously assigned according to the X-ray crystal analysis of compounds **12b**, **14b**, and**17b** (Figure 1).

It is worth mentioning that, for a mixture of diastereomers formed in a Robinson annulation reaction, we can quickly assign the configuration of the one-carbon bridge stereocenter on the basis of the relative positions of NMR signals for the enolic protons and carbons (O_2−H and C_3; see Scheme 3). In each case that we've examined, both the O_2−H and C_3 chemical shifts of the minor diastereomer (*syn*, **a** series) are downfield to those of the major diastereomer (*anti*, **b** series). Another trend that we have observed is that the minor diastereomers are consistently less polar (higher R_f on TLC, shorter retention time in column chromatography) than the major diastereomers. Collectively, this data is consistent with conformational equilibria where the relative stability of

(5) Theobald, D. W. *Tetrahedron* **1969**, *25*, 3139.
(6) (a) Kraus, G. A.; Hon, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 4341. (b) Kraus, G. A.; Hon, Y. S. *Heterocycles* **1987**, *25*, 377.
(7) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1984**, *25*, 4291.

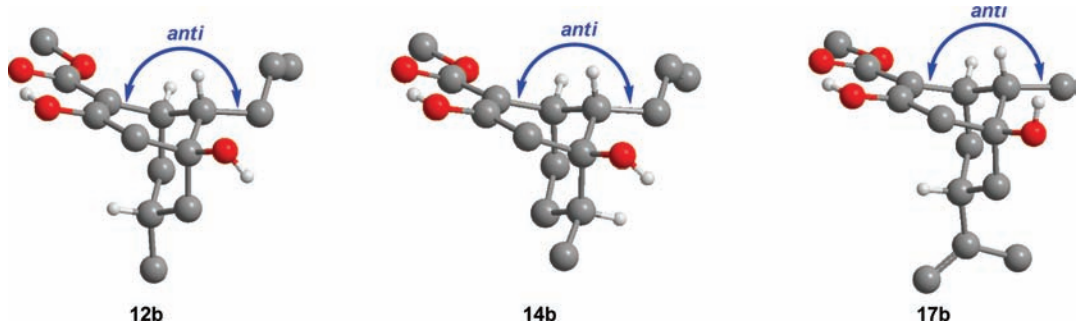
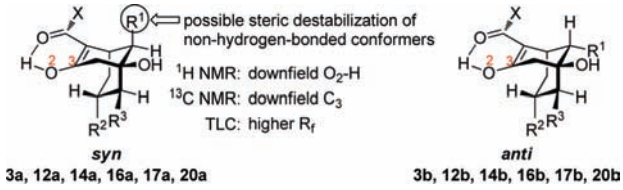


Figure 1. Crystal structures of compounds **12b**, **14b**, and **17b**.

hydrogen-bonded conformers is greater for the minor diastereomers. The one-carbon bridge substituent could influence such an equilibrium by sterically destabilizing non-hydrogen-bonded conformers.

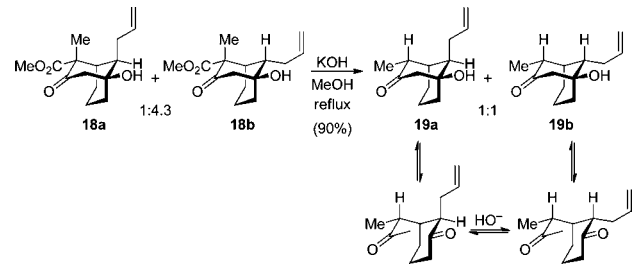
Scheme 3. Comparative Features Allowing Stereochemical Assignment of Diastereomers Formed in the Robinson Annulation



The unanticipated stereoselectivity appears to be kinetically controlled since major *anti* products (**3b**, **12b**, **14b**, **16b**, and **17b**) are higher in energy than diastereomeric minor *syn* products (**3a**, **12a**, **14a**, **16a**, and **17a**). Stereoselectivity also correlates with the expected rate of the aldol ring closure where the major products result from reactions that place the substituent α to the reacting ketone *anti* to the approaching enolate (e.g., **6b** → **3b** in Scheme 2).[11]

While exploring the reaction chemistry of Robinson annulation products, we discovered an interesting epimerization reaction that might provide an alternative stereocontrol motif that can influence the stereochemistry of the substituent at the one-carbon bridge. Treatment of a 1:4.3 mixture of **18a** and **18b**[12] with refluxing methanolic KOH (3 equiv, 24 h) produced a 1:1 mixture of decarboxylation products **19a** and **19b** (Scheme 4).[13] Subjection of diastereomerically pure **19a** or **19b** to the same reaction conditions leads to the same 1:1 mixture, suggesting that the final product ratio represents thermodynamic control. We propose that this isomerization takes place via a retro-aldol reaction followed by base-catalyzed epimerization of the ring-opened diketones.

Scheme 4. Base-Catalyzed Epimerization of the One-Carbon Bridge Stereocenter



A similar base-catalyzed epimerization conducted on a mixture of **3b** and **3a** might change the 4.3:1 **3b**/**3a** kinetic ratio to a thermodynamic ratio favoring the lower energy isomer **3a**. Unfortunately, the base-mediated decarboxylation reaction that takes place under these conditions prevents such an epimerization from being realized. We reasoned that there may be other base-stable electron-withdrawing groups still capable of promoting the enolization that stabilizes the desired diastereomer of the Robinson annulation reaction. Thus, we looked at the Robinson annulation of carvone with acetone derivative possessing an α carbon substituted with either a carboxamide or cyano group. We obtained kinetic product ratios similar to those obtained using β-keto esters (Table 2).

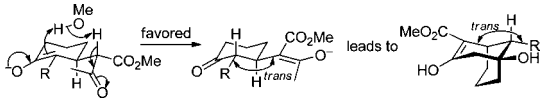
Base-catalyzed epimerization (6 equiv of KOH, refluxing MeOH, 48 h) converted the 2.5:1 **20b**:**20a** β-keto amide

(8) Chong, B.-D.; Ji, Y.-I.; Oh, S.-S.; Yang, J.-D.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323.

(9) Marques, F. A.; Lenz, C. A.; Simonelli, F.; Maia, B. H. L. N. S.; Vellasco, A. P.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 1939.

(10) Kabalka, G. W.; Yu, S.; Li, N. S. *Tetrahedron Lett.* **1997**, *38*, 5455.

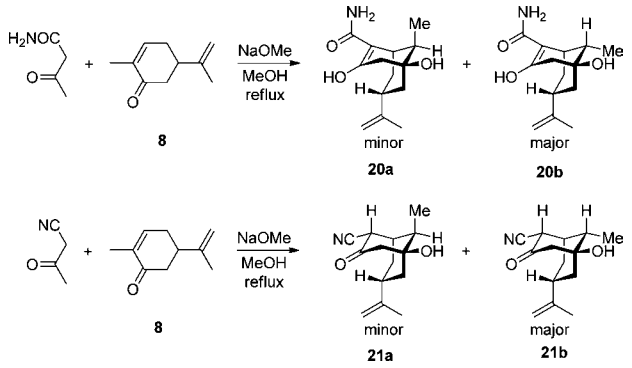
(11) An attractive explanation, suggested by a reviewer, is that observed stereoselectivity could be accounted for by intramolecular proton transfer. A similar stereochemical argument was presented in Grossman, R. B.; Ley, S. V. *Tetrahedron* **1994**, *50*, 11553.



(12) A mixture of **18a** and **18b** was prepared by methylation of the corresponding mixture of **3a** and **3b**.

(13) With less than 3 equiv of base, decarboxylation without epimerization is observed.

Table 2. Robinson Annulation Reactions Aimed at Producing Bicyclo[3.3.1]nonane Products Resistant to Base-Mediated Decarboxylation

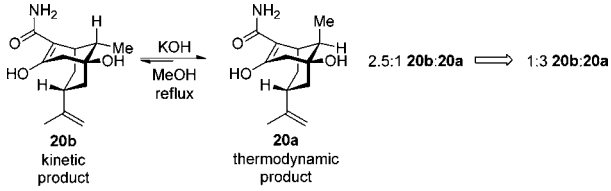


product	ratio (a/b)[a]	total yield (%)
20	1:2.5	80
21	1:2.7	74

[a] The ratio is based upon the ^{1}H NMR of the crude products

mixture obtained from Robinson annulation to a 3:1 **20a**:**20b** mixture (Scheme 5). Base-catalyzed epimerization of pure **20b** produced the same 3:1 mixture where **20a** was the major component.[14]

Scheme 5. Stereoselectivity Reversal via Base-Catalyzed Epimerization



In summary, the one-carbon bridge stereochemistry of bicyclo[3.3.1]nonane systems formed by Robinson annulation has been established, and factors influencing stereoselectivity have been examined. For base-catalyzed reactions conducted under previously reported reaction conditions, we found that the major diastereomer formed places the one-carbon bridge substituent *anti* to the β-keto ester/amide unit introduced in the reaction and stereoselectivity appears to be kinetically controlled. Thermodynamically controlled stereoselectivity can be realized under more forcing conditions in the presence of a large excess of base through an interesting epimerization reaction. In the case of one β-keto amide system that we have investigated, it appears that it may be possible to use base-catalyzed epimerization as a means to reverse the kinetic selectivity obtained in these Robinson annulation reactions thus obtaining the *syn* diastereomer as the major product.

Finally, it should be emphasized that the results presented herein differ from literature precedent in both the sense and the degree of diastereoselectivity, although the reaction conditions employed appear to be identical to those previously reported.[15,16]

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Since the keto form predominated for cyano-substituted Robinson annulation products **21a** and **21b**, an epimerization reaction favoring **21a** was not considered a promising prospect. When the initially attempted epimerization of **21a**:**21b** led to an complex mixture of decomposition products, this reaction was not pursued further.

(15) It is possible that the previously assigned one-carbon bridge configuration[5,6] is incorrect, since product stereochemistry was not confirmed by X-ray crystallography.

(16) Reaction of dimethyl 1,3-acetonedicarboxylate with enals to form bicyclo[3.3.1]nonanes proceeds by sequential Robinson annulations.[3c−e] The second Robinson annulation of this sequence exhibits diastereoselectivity analogous to those described herein, favoring the diastereomer that places the one-carbon bridge substituent *anti* to the β-keto ester unit introduced in the reaction: