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REDUCTIVE CLEAVAGE OF HIGHLY SUBSTITUTED Δ^2-ISOXAZOLINES. SYNTHESIS OF CRISPATIC ACID

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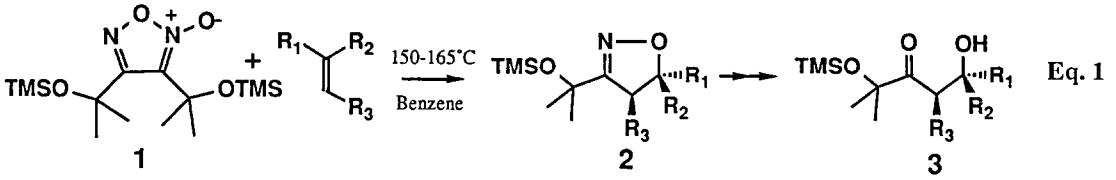
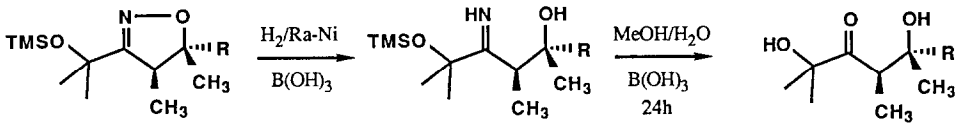
Abstract: The preparation of highly substituted ß-hydroxy carbonyl compounds from isoxazolines is featured in a synthesis of crispatic acid. A ß-hydroxy imine, the proposed intermediate in this transformation, is isolated for the first time and a stereoselective hydroboration of a 5-vinyl substituted isoxazoline is also reported.

The cycloadditive strategy (Eq. 1) for formation of ß-hydroxy carbonyls has begun to emerge as a useful complement to the well established aldol route.[1] One of the strengths of the cycloadditive approach is that it is diastereospecific: in principle, olefin geometry is directly translated into acyclic stereochemistry.[2] The stereocontrolled formation of more highly substituted ß-hydroxy carbonyls by the aldol method can be problematic. Simple diastereoselection in the addition of enolates to ketones is usually low.[3] Furthermore, ketones are not sufficiently reactive partners in many of the mildest cross-aldol variants. In the cycloadditive strategy, access to more highly substituted isoxazolines (2) has also been difficult. We have recently developed a practical method to prepare such isoxazolines using TOP-furoxan (1) as a nitrile oxide source.[4] We now report a synthesis of crispatic acid and its diastereomer which illustrates both the utility of TOP-furoxan to form highly substituted isoxazolines and the ability to selectively reduce these heterocycles to products which are formally stereoselective cross aldol adducts between two ketones. In addition, we report for the first time the isolation of a ß-hydroxy imine, the proposed intermediate in the isoxazoline(2)→ß-hydroxy ketone(3) interconversion. We also report a selective hydroboration of a 5-vinyl isoxazoline.



1 2 3 Eq. 1

To test the applicability of our standard conditions for the cleavage of more highly substituted systems (Eq. 2), TOP-furoxan-trimethylethylene adduct **4a** was reduced with Ra-Ni [$B(OH)_3$, $MeOH/H_2O$, H_2 gas].[1a] After 2h at 25°C, the starting material was consumed and the product was isolated by standard extraction. While the ^1H-NMR multiplicities were consistent with the expected ß-hydroxy ketone **6a**, the IR spectrum showed no evidence of a carbonyl stretch. In fact, the product was the ß-hydroxy imine **5a**. Redissolution of **5a** in $MeOH/H_2O$ containing boric acid and stirring of the mixture for 24h led to the isolation of the dihydroxy ketone **6a** in which both the imine and trimethylsilyl groups had been lost by hydrolysis. While the evidence for the intermediacy of ß-hydroxy imines in the isoxazoline→ß-hydroxy ketone interconversion is very strong[1a], this is the first case in which the proposed intermediate has actually been isolated.[10] Primary imines are very sensitive to hydrolysis and the high degree of substitution no doubt contributes to the unusual stability of **5a**.[5] For cleavage of related systems, a simple protocol was developed. After standard reductive cleavage (1-4h), the Ra-Ni catalyst was removed by filtration and the reaction mixture was allowed to stir for an additional 20-40h to insure complete imine hydrolysis.



4 **a**, R=CH_3 **5** **6**
b, R=CH_2OAc

Eq. 2

While we were pleased to isolate a ß-hydroxy imine intermediate in the isoxazoline reduction, this was not necessarily a good omen for synthetic applications. We had previously demonstrated that stereochemical loss in isoxazoline reductions was due to tautomerization of the transient ß-hydroxy imine.[1a] Furthermore, small amounts of retroaldol products which were formed in several reductions were also suspected of arising from the imine. Clearly, long lifetimes for the intermediate imines are generally not desirable.

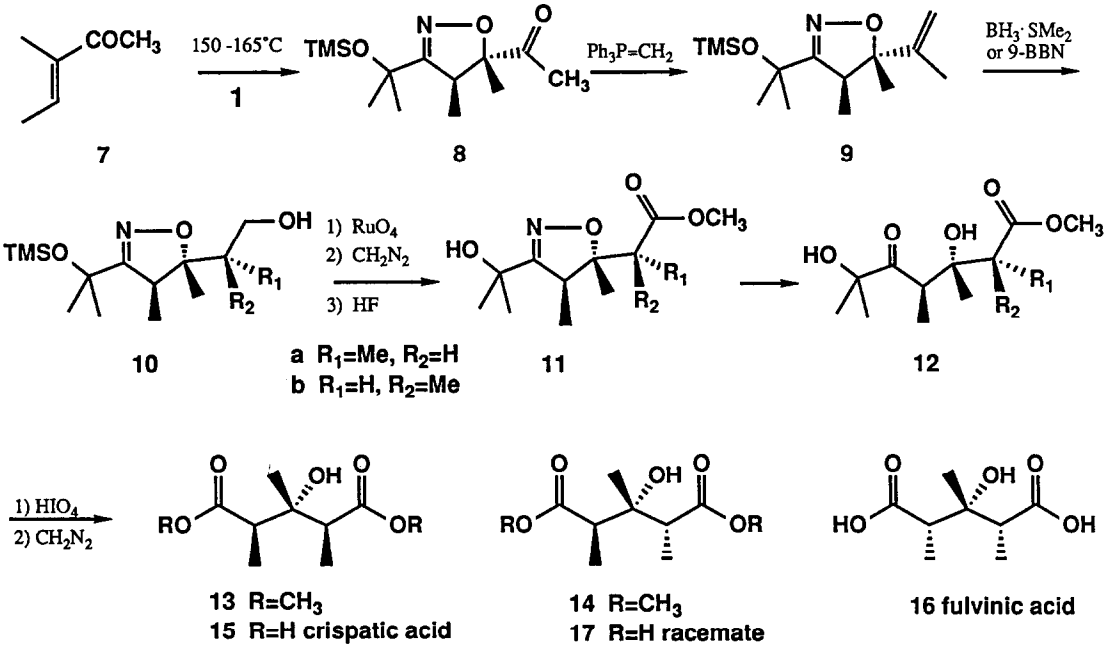
To determine whether the stereochemistry obtained in the cycloaddition reactions of TOP-furoxan with more highly substituted olefins could be retained during reductive cleavage, isoxazoline **4b** was desilylated (HF, MeCN) and reduced as described above. No attempt was made to isolate the intermediate imine. Dihydroxy ketone **6b** was isolated in 58% overall yield from **4b** as a single stereoisomer. Thus, the utility of the cycloadditive strategy has not been compromised by the resistance of the intermediate imine towards hydrolysis in this case.

To demonstrate the synthetic utility of the method (Scheme 1), we undertook the synthesis of crispatic acid,[6] a component of the macrocyclic pyrrolizidine alkaloid crispatine. This target was selected because both other diastereomers, fulvinic acid (a component of the alkaloid fulvine), and **17**, were also known.[6]

Heating of **1** with E-3-methyl-3-penten-2-one (**7**) gave the expected isoxazoline **8** in 60% yield. The geometry of the starting olefin controls the relative stereochemistry at C-2/C-3 and precludes the formation of the diastereomeric isoxazoline leading to fulvinic acid. Standard Wittig olefination provided **9** in 83% yield. Hydroboration of **9** with BH_3/Me_2S gave a nearly 1/1 mixture of diastereomers **10a/10b** in >90% yield. These diastereomers were not readily separable, nor was it possible to assign stereochemistry at this stage. Attempted reduction of bis-O-silylated derivatives of **10** with Ra-Ni proved problematic.[7] Oxidation, diazomethane

esterification, and HF desilylation produced **11** in 40% overall yield from **9**. Hydrogenolytic cleavage as above gave diastereomers **12a/12b** which were separable by chromatography (70% combined yield). No evidence for the presence of other diastereomers was obtained nor were any retroaldol products evident. NMR evidence for the intermediacy of a relatively stable ß-hydroxy imine was again obtained.

Scheme 1



Oxidative cleavage of **12b**, followed by diazomethane esterification, gave crispatic acid dimethyl ester **13**. Independent cleavage of **12a** gave the racemic dimethyl ester **14**. These compounds were readily differentiated by the symmetry properties in the NMR spectra.[8] Additionally, barium hydroxide mediated hydrolysis produced the diacids **15** and **17**, respectively.[6]

In this initial approach, no control over the stereochemistry of the third stereogenic center was observed. In an attempt to improve this situation, we surveyed the reaction of **9** with a variety of hydroborating agents. Interestingly, reduction with 2 equivalents of 9-BBN, followed by standard hydrogen peroxide oxidation, produced only **10a**. Isomer **10b** could not be isolated. Unfortunately, the isolated yield of **10a** could not be raised above 35-40%.[9] While this apparent stereoselectivity is most interesting, we hesitate to attach any significance to this observation at present due to the low yield of **10a**.

In summary, the cycloadditive strategy employing TOP-furoxan has proven useful in the preparation of a highly substituted ß-hydroxyester. Concerns over loss of stereochemical integrity or possible retro aldol reaction in the key reduction step proved unfounded in this instance. While the ability to control the C-2/C-3 relative

stereochemistry was demonstrated, control of the stereochemistry at the third stereogenic center was less than satisfactory. This points to the general need for new methods to control stereochemistry adjacent to the isoxazoline ring in the cycloadditive strategy.

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References and Notes

1) Leading references: a: Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826; b: Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410; c: Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519; d: Ko, S. S.; Confalone, P. *Tetrahedron* **1985**, *41*, 3511; e: Torssell, K. B.; Hazell, R.C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569.

2) In comparison, the aldol approach involves diastereoselectivity. Under kinetic control, the ratio of the diastereomers is determined by the enolate geometry and the relative energies of the transition states. The use of stereospecific versus stereoselective is then meant to convey a fundamental mechanistic difference rather than a level of asymmetric induction.

3) a: Recent aldol reviews: Heathcock, C. H. "Asymmetric Synthesis"; Morrison, J. D., Ed. Academic Press: New York: 1984, Vol. 3, 111; Mukaiyama, T. *Org. React.* **1982**, *28*, 203. b: Most successful diastereoselective aldol reactions with ketone electrophiles have large steric and/or electronic differences between the two substituents. Examples: Bouffard, F. A.; Salzmann, T. *Tetrahedron Lett.* **1985**, *26*, 6285; Fellman, P.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 1349; Stevens, R. W.; Iwasawa, N.; Mukaiyama, T. *Chemistry Lett.* **1982**, 1459; Seebach, D.; Widler, L. *Helv. Chim. Acta.* **1982**, *65*, 1972.

4) Curran, D. P.; Fenk, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 6023. TOP-furoxan=Bis{2-[(trimethylsilyl)-oxy]prop-2-yl} furoxan.

5) Steric bulk on both sides of the C=N is required for isolation of the imine. TOP-furoxan cycloadducts from mono- and disubstituted olefins did not produce observable imines on reduction nor did cycloadducts from trisubstituted olefins and less bulky nitrile oxides. See references 1a and 4.

6) Structures and synthesis: Schoental, R. *Aust. J. Chem.* **1962**, *2*, 233; Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1962**, *2*, 239; Matsumoto, T.; Fukui, K.; Edwards, J. D. Jr. *Chemistry Lett.* **1973**, 283. Total synthesis of crispatine and fulvine: Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030.

7) In several cases, the products of retroaldol reaction were observed or isolated. Problems with bis-O-silylated derivatives may be caused by low solubility of these compounds in the methanol/water reaction mixture. This may suppress the rate of reduction and/or hydrolysis. Consistent with this, better results were obtained with the free alcohols which have more favorable solubility properties.

8) **13**; ^{1}H-NMR ($CDCl_3$) ∂ 3.73 (1H, s), 3.72 (6H, s), 2.66 (2H, q), 1.21 (3H, s), 1.19 (6H, d); ^{13}C-NMR ($CDCl_3$) ∂ 175.9, 74.3, 51.8, 47.0, 19.4, 12.8. **14**; ^{1}H-NMR ($CDCl_3$) ∂ 3.73 (3H, s) 3.71 (1H, s), 3.68 (3H, s), 2.69 (2H, overlapping q), 1.25 (3H, d), 1.20 (6H, overlapping s and d); ^{13}C-NMR ($CDCl_3$) ∂ 177.0, 175.7, 73.7, 47.6, 45.2, 20.2, 12.8, 12.0.

9) No reduction was observed with only one equivalent of 9-BBN. At least two other minor products were formed which possibly resulted from C=N reduction but these were not characterized. Thexyl borane and dicyclohexylborane did not give satisfactory reduction. For osmylations and epoxidations of 5-vinyl isoxazolines see ref. 1e and: Annunziata, R.; Cinquini, M.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217.

10) After the acceptance of this manuscript, a report on the isolation of a ß-hydroxy imine has appeared: Baraldi, B. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc. Chem. Commun.* **1986**, 757.

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