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Promoter-Dependent Course of the Beckmann Rearrangement of Stereoisomeric Spiro[4.4]nonane-1,6-dione Monoximes

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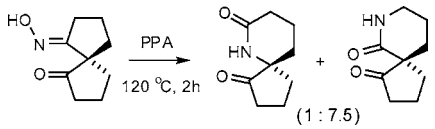
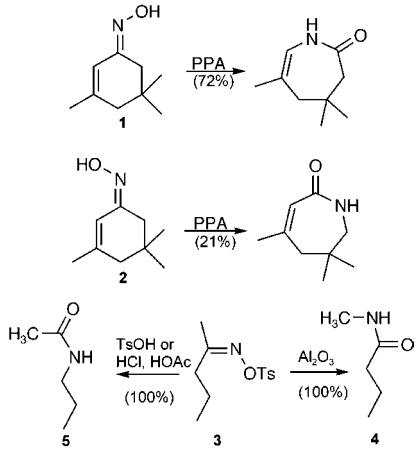
ABSTRACT



Activation of the Beckmann rearrangement of the enantiopure spirocyclic keto oximes (–)-9 and (–)-12 has been initiated with four acidic promoters. In two cases (PPE and PPSE), concerted 1,2 shift of the anti carbon operates exclusively. This is not the case with PPA or Eaton's reagent, although optical activity is fully maintained in these ring expansions as well.

The stereospecificity normally associated with the Beckmann rearrangement has long served the adaptation of this transformation in synthesis.[1] Justifiably, heavy reliance has often been placed on controlled migration of the group positioned anti to the X substituent departing from nitrogen as with **1** and **2**.[2] A very few apparent exceptions have, however, been documented. One such example is represented by (*Z*)-2-pentanone oxime (**3**). Recourse to alumina as the promoter delivers **4** in expected fashion. In contrast, the action of protic acid on **3** eventuates in exclusive conversion to **5**, presumably as the result of prior isomerization to the *E*-isomer.[3]

The recent discovery of the marine alkaloids pinnaic acid (**6**)[4] and halichlorine (**7**)[5] has prompted us to consider an enantioselective route to these structurally intricate 6-azaspiro[4.5]decanes[6] that is based on lactam **8** (Figure 1). The acquisition of **8** was contemplated to arise from Beckmann rearrangement of the enantiomerically pure compound **9**. This type of ring expansion has been minimally applied to spirocyclic systems because of their propensity for fragmentation[7] or rearrangement−cyclization.[8] Beyond this, β-keto



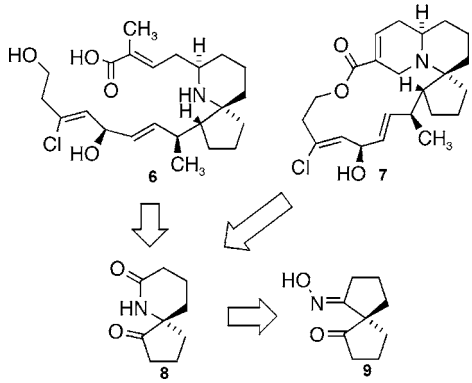


Figure 1.

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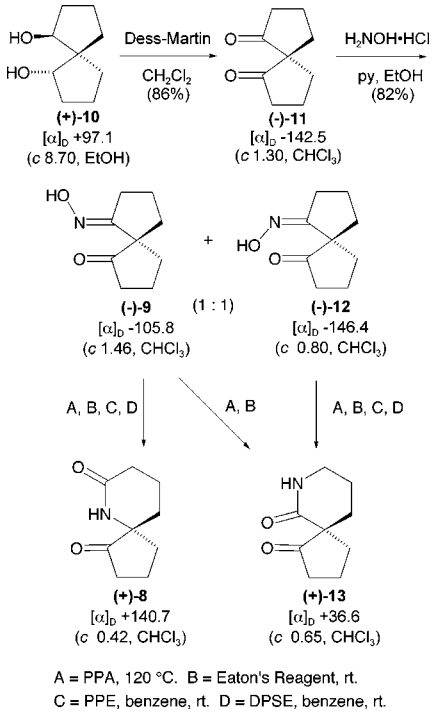
oximes have been scrutinized in only a very limited way.[9] Herein, we record several specific features associated with proximal positioning of a carbonyl group to the spirocyclic center and detail an unexpected interdependency involving the acid initiator and ultimate migratory pathway.

Oxidation of the known dextrorotatory diol **10**[10] with the Dess−Martin periodinane[11] furnished (−)-diketone **11** in good yield (Scheme 1). Subsequent heating of (−)-**11** with hydroxylamine hydrochloride in ethanol containing pyridine gave rise to a chromatographically separable 1:1 mixture of (−)-**9** and (−)-**12**. As a direct consequence of the C_2 symmetry about the quaternary carbon in **11**,[12] the particular carbonyl group undergoing oximation is irrelevant. The syn and anti configurational assignments to the monoximes rest on their ring-expansion chemistry (to be detailed below) and additional intercorrelation with (+)-**8**.[13,14]

At this point, we addressed the response of **9** and **12** to the action of PPA,[15] Eaton's reagent,[16] PPE,[17] and PPSE[18]

Scheme 1



(Table 1). In the presence of polyphosphate ester or polyphosphate silyl ester, the isomeric oximes underwent stereospecific rearrangement to form (+)-**8** and (+)-**13**, respectively. The yields given by PPE were notably superior. Chiral HPLC analysis demonstrated that the integrity of the stereogenic center of the spirocyclic core was fully preserved during the concerted 1,2-shift. In striking contrast, the use of PPA as promoter resulted in the formation of (+)-**13** (predominantly from (−)-**9** or exclusively from (−)-**12**). This departure from the norm is observed to a lesser extent with Eaton's reagent. These data provide decisive insight into the fact that not all acidic Beckmann initiators are equivalent. Polyphosphoric acid gives evidence of inducing the most extensive departure from anti migration. No loss of optical activity was evident for either product in entries 1−8.

Table 1. Acid-Promoted Beckmann Rearrangements of (−)-**9** and (−)-**12**[a]

entry	keto oxime	promoter	lactam product(s)	yield,%
1	(−)-**9**	PPA	(+)-**8**, (+)-**13**	4, 30
2	(−)-**12**	PPA	(+)-**13**	23
3	(−)-**9**	Eaton	(+)-**8**, (+)-**13**	25, 8
4	(−)-**12**	Eaton	(+)-**8**	20
5	(−)-**9**	PPE	(+)-**8**	70
6	(−)-**12**	PPE	(+)-**13**	70
7	(−)-**9**	PPSE	(+)-**8**	19
8	(−)-**12**	PPSE	(+)-**13**	34

[a] Product analysis was accomplished by analytical HPLC on a Chiralpak AD column using either 25% or 60% ethanol in hexanes. The following retention times were recorded; (+)-**8**, 12.8 min; (−)-**8**, 20.8 min; (+)-**13**, 12.7 min; (−)-**13**, 11.0 min. No racemization was operational in all eight examples documented here.

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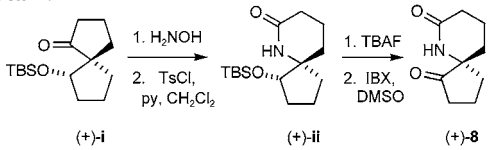
(14) Chemical intercorrelation was also achieved by transforming **i** exclusively via its anti oxime to **ii**, followed by desilylation and oxidation of this lactam:



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The present study has demonstrated a direct link between the structural features of possible lactam products and the specific promoter employed for the Beckmann reaction. Although this interrelationship is not commonly seen, its incursion in spirocyclic substrates can be triggered under controlled conditions. While the present observations may be regarded by some as the breakdown of an often stereospecific process, we prefer to view these exceptions as an opportunity to expand the utility of this rearrangement into yet unexplored areas. In this regard, the full retention of optical activity in all products holds particular attraction.

Supporting Information Available: Experimental details and ^{1}H NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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