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Unified Synthesis of $C_{19}-C_{26}$ Subunits of Amphidinolides B_1, B_2, and B_3 by Exploiting Unexpected Stereochemical Differences in Crimmins' and Evans' Aldol Reactions

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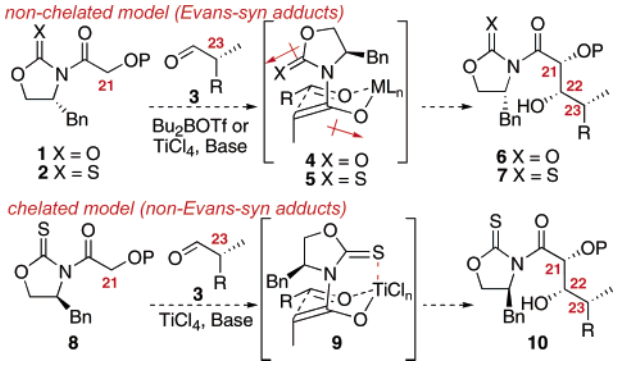
Abstract: The efficient synthesis of the $C_{19}-C_{26}$ subunit of amphidinolide B_1 and B_2 has been completed using a boron-mediated aldol reaction. The synthesis of the $C_{19}-C_{26}$ subunit of amphidinolide B_3 has also been accomplished through an unexpected anti aldol reaction using a titanium-mediated process. In addition, the first reported examples of a stereochemical discrepancy between the Evans' boron-mediated oxazolidinone and the Crimmins' titanium-mediated oxazolidinethione aldol reactions are disclosed. A working hypothesis is put forth to explain the results.

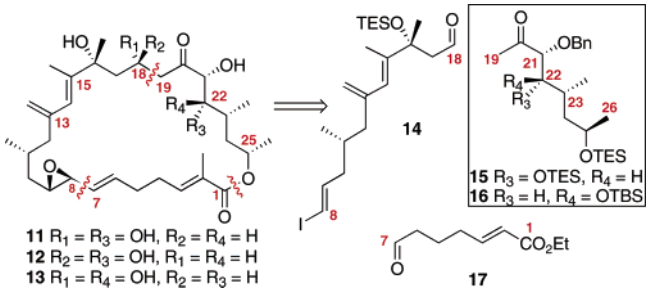
The synthetic utility of chiral oxazolidinones has been well-documented in the organic community.[1] This powerful removable auxiliary has been shown to be effective in the construction of a wide variety of carbon−carbon and carbon−heteroatom bonds in a highly stereoselective fashion. Numerous working models have been put forth to explain and predict the resultant stereochemical outcome from these reactions. These models have proven to be highly reliable and general, with only isolated examples of anomalies having been reported.[2]

In particular, the so-called "Evans-syn" aldol reactions with chiral oxazolidinones using dibutylboron triflate and the appropriate amine base have become the standard by which new asymmetric and diastereoselective reactions are judged against (Scheme 1).[3] The recently developed titanium-mediated oxazolidinethione aldol reaction, from the Crimmins laboratory, has been shown to provide comparable levels of selectivity on a wide range of systems.[4] There are several advantages to the Crimmins' aldol methodology (e.g., relative ease of auxiliary cleavage and use of the logistically easier titanium enolates). One particularly attractive attribute is the flexibility imparted by Crimmins' chelated and nonchelated models which is dependent on the amount of $TiCl_4$ and

SCHEME 1. Generalized Examples of Crimmins' and Evans' Aldol Adducts



SCHEME 2. Retrosynthetic Analysis of Amphidinolide B_1



amine base (normally (−)-sparteine) that is added. This modification provides access to both the Evans-syn product via the nonchelated model and the non-Evans-syn adduct via the chelated model (Scheme 1). The level of syn/anti selectivity is high (normally > 20:1) and comparable to traditional boron-mediated aldol reactions for both the chelated and nonchelated titanium-mediated conditions. It should be pointed out that Crimmins has shown that the chirality of (−)-sparteine does *not* influence the stereochemical outcome of the transformation.[4]

We were attracted to the application of the Crimmins and/or Evans methodologies for the construction the eastern subunit **15** of the cytotoxic macrolide amphidinolide B_1 (**11**)[5,6] (Scheme 2). Amphidinolide B_1 has attracted considerable synthetic interest,[7] yet the total synthesis of **11** remains an elusive target.[8] Two additional members of the amphidinolide B family, B_2 (**12**) and B_3 (**13**), have also been reported. These structures only differ from the parent B_1 structure by alternate stereochemistries at C_{18} and/or C_{22}. Compounds **11** and **12** should be accessible from a common subunit **15** while C_{22} epimer **13** should be accessible from the *anti*,*anti* adduct **16**.

While the application of the titanium-mediated aldol methodology has begun to appear,[9] several important combinations have yet to be fully explored. One such example is the coupling of an *O*-benzyl-protected glyco-

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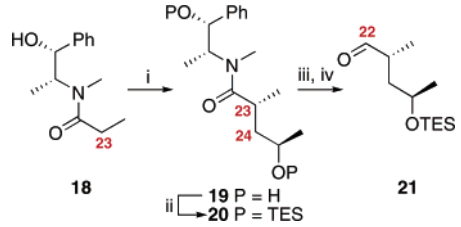
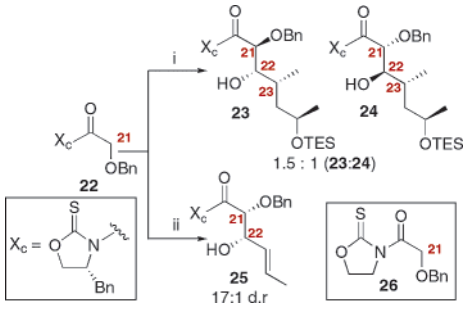
SCHEME 3[a]



[a] Key: (i) ref 11, (*R*)-propylene oxide, 92%, 94:6 dr; (ii) TESCl, Et_3N, DMAP, CH_2Cl_2; (iii) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C, 78% over two steps; (iv) TPAP, NMO, CH_2Cl_2, 85%.

SCHEME 4[a]



[a] Key: (i) $TiCl_4$ (1 equiv), (−)-sparteine (2.5 equiv), **21**, CH_2Cl_2, 0.15 M, −78 °C, 40 min, 1.25:1 dr (**23**:**24**), 44% **23**, 30% **24**; (ii) $TiCl_4$ (1 equiv), (−)-sparteine (2.5 equiv), 2-butenal, CH_2Cl_2, 0.15 M, −78 °C, 40 min, 80%.

late such as **2** or **8** with an α-chiral aldehyde **3** to provide a *syn*,*syn* coupled adduct such as **7** or **10** (Scheme 1). The stereochemical "Felkin" relationship of the C_{22} and C_{23} positions (amphidinolide B_1 numbering) would appear to be ideally suited for this transformation as both the auxiliary and the aldehyde appear to be directing the outcome in a complementary fashion. Despite this combination, the examples of a *syn*,*syn* adduct from an *O*-benzyl-protected glycolate such as **1**, **2**, or **8** are surprisingly rare.[10] In fact, no examples of the aldol reaction depicted with oxazolidinethione **2** or **8** have been reported with α-chiral aldehydes. In this paper, we disclose the first reported examples of these combinations and the resulting synthesis of the $C_{19}-C_{26}$ subunits **15** and **16** for all amphidinolides B_1-B_3.

Construction of the necessary aldehyde precursor **21** was accomplished in four steps from commercially available Myers auxiliary **18**. The known alkylation[11] with the commercially available (*R*)-propylene oxide provided the $C_{23,24}$-coupled material **19** in 94:6 dr.[12] Subsequent TES protection followed by reduction with $BH_3{\cdot}NH_3$/LDA and Ley oxidation[13] yielded the desired aldehyde **21** (Scheme 3).

Exploration into the aldol reaction commenced with the known oxazolidinethione auxiliary **22**[14] (Scheme 4). Treatment of the prescribed conditions for obtaining nonchelation or "Evans-*syn*" aldol adducts [$TiCl_4$ (1.0 equiv), (−)-sparteine (2.5 equiv)] provided two diastereomeric aldol adducts **23** and **24** in a 1.5:1 ratio. Unlike as predicted in the Crimmins' models for this transformation, *none* of the expected Evans-*syn* adduct was observed. Instead, the *anti* adducts **23** ($H_{21}-H_{22}$ J = 9.3 Hz) and **24** ($H_{21}-H_{22}$ J = 8.4 Hz) were isolated in nearly equal amounts.[15] The addition of additives such as NMP or alternate bases (e.g., TMEDA) did not affect the observed stereochemical outcome.[4] Thwarted by this unexpected result, we turned to an achiral aldehyde (2-butenal) to ensure the protocol was performing as expected. Aldol reaction under the identical conditions [$TiCl_4$ (1.0 equiv), (−)-sparteine (2.5 equiv)] provided solely the expected Evans-*syn* adduct **25** ($H_{21}-H_{22}$ J = 3.3 Hz) in a 17:1 ratio. One possible explanation would be a mismatched relationship between the directing effect of the auxiliary and the inherent stereochemical preference of the aldehyde. To this end, the experiment was conducted with the achiral auxiliary **26**; however, equal amounts of the two previously observed *anti* stereochemistries (21*R*,22*R* and 21*S*,22*S*) were again the only observable products.

Given that the nonchelation approach provided none of the desired syn adduct (e.g., compound **7**), the complementary chelation aldol would appear to be the next logical step (Scheme 5). Using the enantiomeric oxazolidinethione auxiliary **27**, treatment under the chelation conditions [$TiCl_4$ (2 equiv), (−)-sparteine (1 equiv)] proceeded poorly and in low yield. Crimmins has also reported that the use of less $TiCl_4$ [(1 equiv), (−)-sparteine (1 equiv)] proceeds via the chelated model.[4] Treatment using these conditions provided some improvement in the selectivity of the transformation, yielding a more respect-

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(10) Only four reported examples of this combination have appeared in the literature: (a) Crimmins, M. T.; Katz, J. D.; McAtee, L. C.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949−52. (b) Chakaborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775−78. (c) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617−18. (d) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998−3017.

(11) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428−40.

(12) It should be noted that this stereochemical combination provides the epimeric stereochemistry at C_{25} versus the target **11**; however, the alkylation of the enantiomeric (*S*)-propylene oxide proceeds in poor selectivity due to its mismatched relationship to the approaching enolate. This stereocenter will be inverted later in the synthetic sequence.

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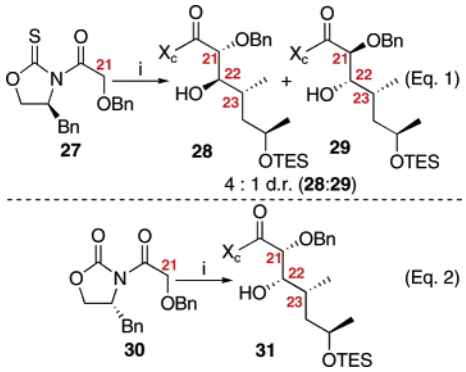
(14) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591−94.

(15) It should be noted that Crimmins has recently reported the development of a titanium-mediated oxazolidinethione method for the synthesis of *anti* aldol adducts through an open transition state; however, this reaction protocol requires the addition of an additional 2.5 equiv of $TiCl_4$ immediately prior to addition of the aldehyde. See ref 14.

SCHEME 5[a]



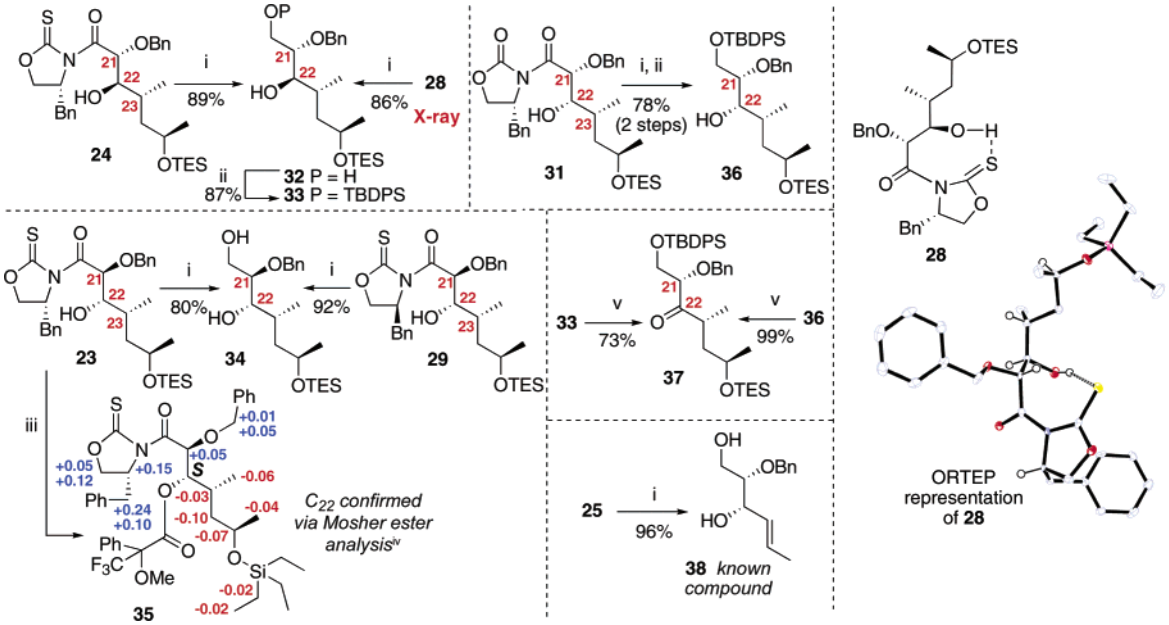
[a] Key: (i) $TiCl_4$ (1 equiv), (−)-sparteine (1 equiv), **21**, CH_2Cl_2, 0.15 M, −78 °C, 40 min, 4:1 dr (**28**:**29**), 53% **28**; (ii) Bu_2BOTf (1 equiv), Et_3N (1.1 equiv), PhMe, 0.15 M, −50 to −30 °C, 2 h, 72%.

able 4:1 ratio of the two *anti* products (**28**/**29**) (**28**: H_{21}−H_{22} J = 8.8 Hz; **29**: H_{21}−H_{22} J = 9.2 Hz) with *none* of the predicted syn adduct. It is important to note that despite the expected directing effect of the auxiliary (e.g., **22** should give the same absolute configuration at C_{21}, C_{22} under nonchelation conditions as enantiomeric auxiliary **27** gives under chelation conditions), the major product **28** from the chelation-controlled conditions using **27** contained the 21*R*,22*R* stereochemistry of the **minor** product from the nonchelation conditions with **22**. Alcohol **28** is synthetically useful as it possesses the correct *anti*,*anti* C_{21-23} stereochemistry for amphidinolide B_3. Interestingly, use of the enantiomeric auxiliary **22** under chelation conditions led to an equal mixture of the adducts **23** and **24**. A similar result was observed with the achiral auxiliary **26**. It became apparent at this juncture that the titanium-based aldol were unable to provide the necessary stereochemical relationship (e.g., **7** or **10**) for amphidinolides B_1 and B_2. We were gratified to observe that use of the auxiliary **30**[16] under boron-mediated conditions did yield the desired Evans-*syn* adduct **31** (H_{21}−H_{22} J = 2.1 Hz) in a 95:5 *syn*,*syn* and *syn*,*anti* ratio (72% isolated yield of **31**). *To the best of our knowledge, these results represent the first reported examples of the stereochemical divergence between the titanium-mediated oxazolidinethiones and boron-mediated oxazolidinones.*[15]

Stereochemical assignment of the aldol products **23**−**25**, **28**−**29**, and **31** was accomplished via a series of degradation experiments and X-ray crystallographic analysis of **28** (Scheme 6). Reductive removal of the auxiliaries from adducts **24** and **28** yielded an identical diol **32**, thereby confirming **24** vis-à-vis X-ray structure **28**. An analogous path was followed for the adducts **23** and **29** to yield the diol **34**. The stereochemistry of **31** was confirmed via conversion to the TBDPS ether **36** and correlation with the TBDPS ether **33** through TPAP oxidation to the ketone **37**. This degradation also indirectly established one of the two unknown stereocenters of **23** and **29** as 21*S* by assignment of both aldol adducts **28** and **31** as the 21*R* configuration. The 22*S* configuration was confirmed by Mosher ester analysis of **35**.[17] Finally, the stereochemistry of **25** was confirmed by reduction to a known compound **38**.[18]

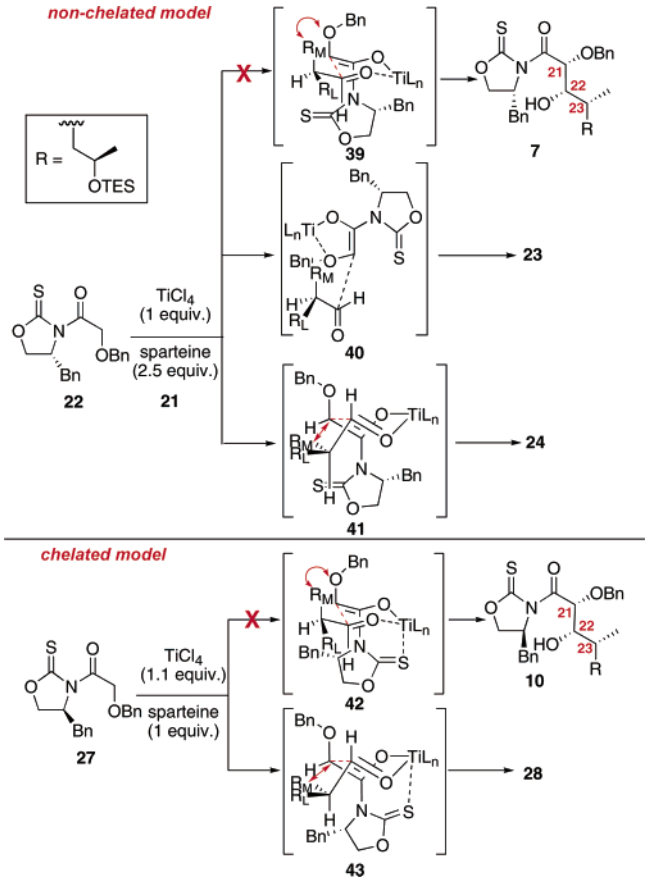
A working hypothesis for the observed stereochemical results invokes the use of the open transition state **40** and boat transition states[19] **41** and **43** to explain the observed stereochemistry (Scheme 7). One possible rational for the inability of these transformations to proceed through the chair transition states **39** and **42** could be an unfavorable interaction between the benzyloxy substituent and the α-position of the aldehyde.[20] As steric bulk at these positions increase, this unfavorable interaction should become more significant. We also hypothesize that the bulk of the benzyloxy substituent may be increased by an aggregation effect. While additional studies

SCHEME 6[a]



[a] Key: (i) $LiBH_4$, MeOH, THF, 0 °C to rt; (ii) TBDPSCl, imid, DMAP, CH_2Cl_2, 0 °C to rt; (iii) (*R*)/(*S*) Mosher acid chloride, DMAP, CH_2Cl_2; (iv) difference in ppm [(*S*)-Mosher ester−(*R*)-Mosher ester, $CDCl_3$, 400 MHz NMR] shown on structure **35**; (v) TPAP, CH_2Cl_2, molecular sieves.

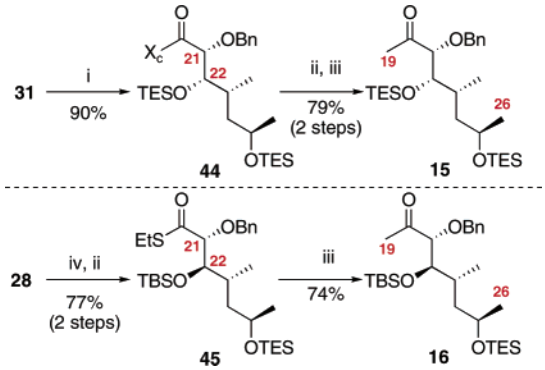
SCHEME 7. Possible Explanation for Observed Stereochemical Outcome



are necessary to verify this aggregation effect, we do observe a modest correlation of concentration with diastereoselectivity [0.15 M, 4:1 dr; 0.05 M, 2:1 dr (**28**:**29**)]. A similar correlation is observed for this transformation by even a slight variation in the ratio of auxiliary to aldehyde. The use of 1.5 equiv of auxiliary **27** with 1 equiv of the aldehyde **21** yielded a 4:1 ratio (**28**/**29**), while 2.0 equiv of the same auxiliary **27** (1 equiv of **21**) yielded a 2:1 ratio (**28**/**29**) under the described chelation conditions. Phillips and co-workers have also commented on the sensitivity of titanium-mediated aldol reactions to slight modifications.[19a] In contrast to the titanium enolates, the boron enolates are unable to aggregate in the Zimmerman−Traxler transition state due to the full valence shell on boron. This important difference does appear to agree with the observed stereochemical results. Finally, an open transition state **40** is put forth to justify the anti adduct **23**.[15] This proposed explanation allows for an approach of the aldehyde consistent with the Felkin model.

Completion of the C_{19}−C_{26} subunits of amphidinolide B_1−B_3 was accomplished in three steps (Scheme 8). Silylation using TESOTf provided the bissilylated compound **44**. Conversion to the thioester using catalytic amounts of KSEt followed by cuprate coupling gave the methyl ketone **15**.[21] An analogous path was pursued with *anti*,*anti* adduct **28** to provide the methyl ketone **16**. Interestingly, attempted introduction of TBS protecting group on the adduct **31** led to competitive silyl migration. This migration was not observed with the adduct **28**.

SCHEME 8[a]



[a] Key: (i) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) EtSH, KH (cat.), THF; (iii) Me_2CuLi, Et_2O, −50 °C; (iv) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

A unified strategy for the synthesis of the C_{19}−C_{26} subunits of amphidinolide B_1−B_3 **13**−**15** has been accomplished. The first reported examples of the divergence of the titanium-mediated oxazolidinethione aldol reaction to provide the anti adducts **23**−**24** and **28**−**29** as the sole products have been reported. A working model is put forth to explain the stereochemical results.

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Supporting Information Available: Crystallographic data for aldol adduct **28** and experimental procedures, including copies of spectral data (^{1}H and ^{13}C NMR), for compounds **15**, **16**, **21**, **23**−**25**, **28**, **29**, **31**−**34**, **36**−**38**, **44**−**46**, and **49**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Reduction using lithium borohydride revealed the known diol which match the reported ^{1}H NMR and ^{13}C NMR spectrum. [$[\alpha]^{20}_D$ = +17.5 (*c* = 0.48, $CHCl_3$) vs lit. +16.8 (*c* = 2.0 in $CHCl_3$)]. Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2743−46.

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(20) For recent and somewhat related examples, see: (a) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761−65. (b) Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577−82.

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