Mechanistic Studies

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On the Rearrangement of an Azaspiroindolenine to a Precursor to Phalarine: Mechanistic Insights**

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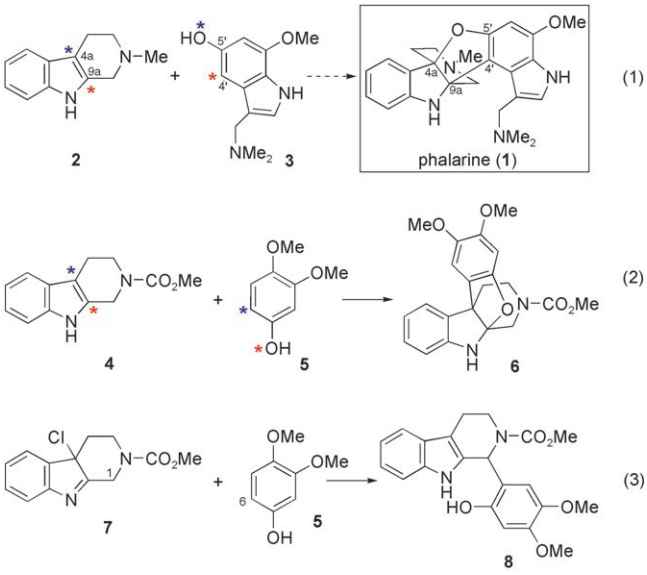
In an agronomy-centered investigation directed at the suitability of *Phalaris coerulescens* (blue canary grass) for introduction into Australia, Colegate and co-workers isolated a furanobisindole alkaloid which they termed phalarine.[1] On the basis of spectroscopic analysis, in particular NMR and MS, the structure of phalarine was assigned as **1** (Scheme 1). This representation was not supported by systematic degradation, let alone corroboratory crystallographic studies. Given our long term involvement in novel indole alkaloids,[2] we took an interest in the structure **1** proposed for phalarine, and began to formulate possible routes for its total synthesis.



Scheme 1. Original strategy toward phalarine.

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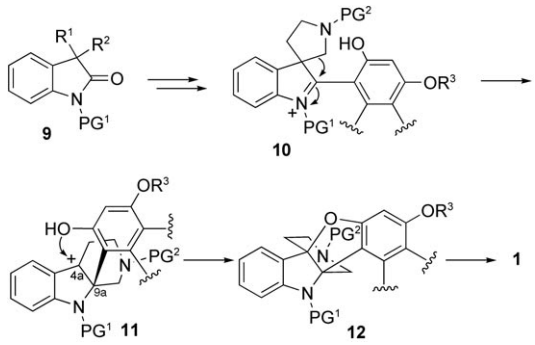
In the early stages, our thinking was influenced by the isolation of *N*-methyl-β-carboline (**2**) together with phalarine,[3] which led to proposals to account for its biosynthesis, and, by extension, ideas for its chemical synthesis (Scheme 1). It was conjectured, both for the biogenesis and chemical synthesis, that oxidative heterocoupling of **2** with a suitable derivative of 5-hydroxygramine (**3**) could lead to a phalarine-like structure. To reach phalarine would require the sites of **2** and **3** marked by asterisks to be connected (red to red, blue to blue) in some manner (Eq. (1) in Scheme 1). Our first thought was to simulate such a biogenesis. In fact we never explored this invitingly simple notion for the synthesis in the context of the mature structures **2** and **3**. Rather, the central idea was first evaluated with the seemingly relevant models (**4** and **5**). While we did indeed realize the oxidative heterocoupling of **4** and **5**, we were unable to do so in the manner required for phalarine. Thus, as previously reported,[4] oxidative coupling of these two compounds produced compound **6** (see alternative positions of asterisks, Eq. (2), Scheme 1). As a further complication, an affinity between the benzyl C1 atom of the carboline and the C6 atom of the phenol served to overwhelm a potential alternative solution (see **7**+**5**→**8**, Eq. (3), Scheme 1).[5,6]

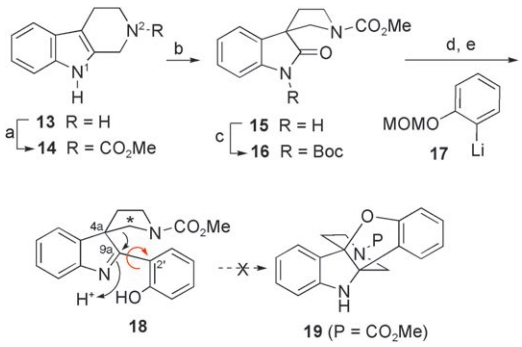
On the basis of these and numerous other setbacks, we decided that prospects for success could well require a substrate in which the C–C bond between the α-carbon atom of the indole (C9a, phalarine numbering) and the *O*-hydroxyaryl moiety (C4′) would be securely in place prior to the reactions which would set up the linkage of the phenolic oxygen atom to the β-carbon atom of the carboline (C4a). Of course, this prospectus would mean forgoing the option of passing through a readily synthesizable β-carboline derivative, such as **2,** in the oxidative coupling itself. Rather, in our new route, the carboline moiety would be constructed on-site by ring expansion of an azaspiroindolenine structure such as **10** (Scheme 2). Indeed, we envisioned that the rearrangement step that would fashion the hexahydrocarboline framework would itself create a positive charge at the β-carbon atom of the indoline, thereby setting the stage for the critical O–C4a bond formation which had eluded us. We further conjectured that an azaspirooxindole system such as **9**, albeit with as yet unspecified protecting groups on the two nitrogen atoms, would serve as a matrix from which to reach azaspiroindolenine **10**. Herein we report on the development of this new strategy, which led to the desired rearrangement of an azaspiroindolenine to give the precursor of phalarine, and thus subsequently enabled the inaugural total synthesis of phalarine.[7]

We began our study with the hope of examining the proposed rearrangement in the context of the azaspiro-



Scheme 2. Modified strategy toward phalarine. PG = protecting group.

indolenine structure **18**, which we expected would rearrange to **19** (Scheme 3). This reasoning led us back to the simple β-carboline **13**, which was converted into **14** and then, by a well-precedented NBS-induced oxidative rearrangement, to

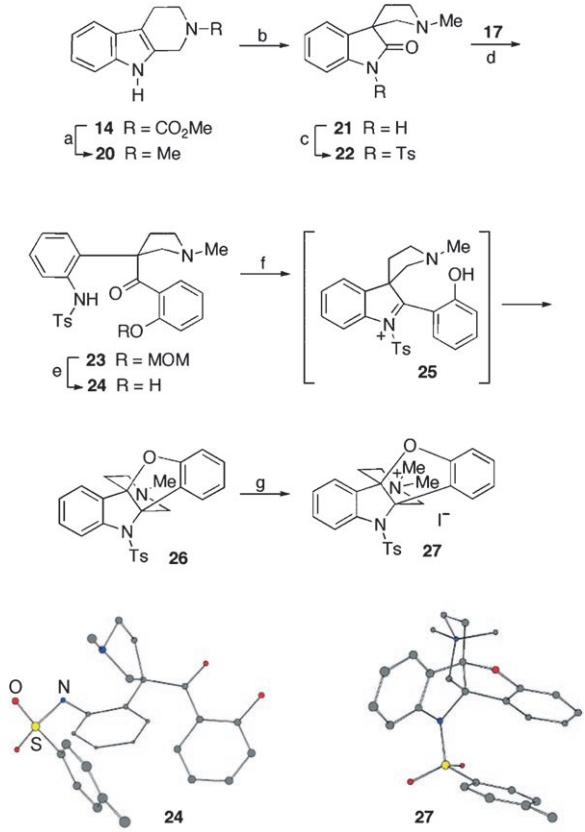


Scheme 3. Reagents and conditions: a) methyl chloroformate, CH_2Cl_2/sat. aq $NaHCO_3$ (1:1), RT, 99%; b) NBS, THF/H_2O then AcOH, 0°C, 84%; c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 84%; d) **17**, *t*BuLi, THF, −78°C; e) TFA, CH_2Cl_2, 54% (2 steps). NBS = *N*-bromosuccinimide, Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, MOM = methoxymethyl, TFA = trifluroacetic acid.

spirooxindole **15**.[8] Following a further carbamoylation, we had the bisurethane **16** in hand. Coupling **16** with the aryl lithium **17** gave a 1:1 adduct, which, on treatment with trifluoroacetic acid, afforded imine **18**. Surprisingly, all attempts to achieve the rearrangement of **18** to the desired model product system **19** were unsuccessful. Remarkably such attempts, under a range of conditions, led primarily to the recovery of **18**.

Several possibilities could account for the failure of this seemingly straightforward rearrangement (**18**→**19**) to progress. First, the migratory aptitude of the urethane-bound methylene carbon atom (see asterisk, **18**, Scheme 3) of the spiroazaoxindole could be rather low, when attached to a ureido-type nitrogen atom.[9] Moreover, hydrogen bonding between the phenolic function and the nitrogen atom of indolenine could restrict the free rotation around the C9a–C2′ bond.[10] Such a rotation is likely to be vital to the establishment of the phenyl ether–C4a bond (phalarine numbering), which is needed to drive the ring-expanding rearrangement step in the direction of the precursor to phalarine. In future studies, it will be interesting to further investigate the individual factors contributing to the failed conversion of **18** into **19**. However, for purposes of the synthesis, we focused instead on the identification of an optimal system which might undergo the critical rearrangement step, thus validating the central idea and enabling convergence on phalarine itself.

To meet this goal, we concentrated on gaining access to **25**, or a functional equivalent thereof (Scheme 4). This structure would contain an activating tosyl function at the N1-position,



Scheme 4. Reagents and conditions: a) $LiAlH_4$, THF, 99%; b) NBS, THF/H_2O/AcOH (1:1:1.5), RT, 79%; c) LiHMDS, TsCl, THF, 0°C, 89%; d) **17**, *n*BuLi, THF, −78°C, 94%; e) TFA, CH_2Cl_2, 0°C to RT, 95%; f) CSA, $PhCH_3$, 150°C, 52%; g) MeI, benzene, 60% conv. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, Ts = *para*-toluenesulfonyl, CSA = (±)-camphorsulfonic acid.

and an *N*-methyl function at the N2-position of the azaspiroindolenine. Fortunately, the carbomethoxy group of **14** could be converted into the *N*-methyl tertiary amine **20** (Scheme 4). An oxidative rearrangement of **20** mediated by NBS afforded **21**,[8] which, on tosylation of the N1-position, gave rise to **22**. Arylation of **22** with **17** led to the 1:1 adduct **23**. Removal of the MOM ether afforded ketone **24**, whose structure was confirmed by X-ray analysis.[10] While at the planning stage we had been thinking in terms of **25** (or its hydrate precursor) as the substrate that would undergo rearrangement, we anticipated that the tosyliminium linkage, which would provoke rearrangement, would still be accessible by progression from **24**.

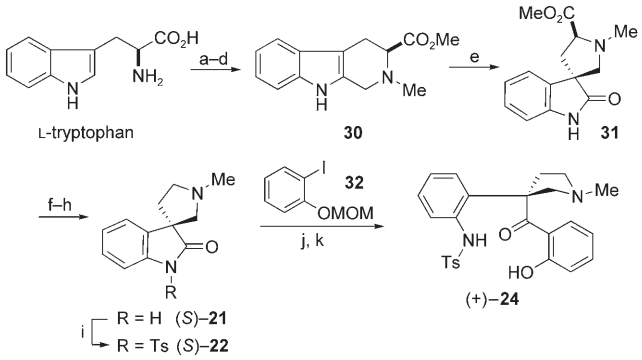
In the event, treatment of **24** with camphorsulfonic acid at 150°C afforded **26** in 52% yield, presumably via an inter-

mediate such as **25**. The structure assignment of **26** was confirmed by X-ray analysis of its methiodide derivative **27**.[10] Thus, with proper substitution, the hypothesized rearrangement of azaspiroindolenine **25** to the precursor to phalarine **26** was indeed realizable.

In the following Communication,[7] we will show how this core chemistry, appropriately modified, enabled realization of our goal, namely, the total synthesis of phalarine. Herein, we concentrate on some subtle issues which we found to be fascinating in their own right, especially in regard to their impact on broad issues in the chemistry of extended indoles.

From the presumed intermediate **25**, one could, in principle, formulate two separate mechanistic interpretations to account for progression to **26**. The first (path a, Scheme 5) would entail a Wagner–Meerwein-like 1,2-shift, which is expected to proceed in a suprafacial fashion.[11] Following O–C4a bond formation, structure **26** would emerge. In an alternative pathway (path b), **25** would first undergo a retro-Mannich reaction.[12] The ensuing achiral intermediate **28** would be susceptible to the Pictet–Spengler reaction,[13] thus providing the carbocation **29**. The latter would be well-disposed to undergo attack by the resident phenolic functionality, ultimately providing the observed rearrangement adduct **26**.

Inspection of these two mechanistic pathways reveals a distinction which can, in principle, be tested. In the Wagner–Meerwein-like pathway (path a), there is a chirality transfer between C4a and C9a in going from **25** to **26**. By contrast, path b proceeds via the achiral intermediate **28**. Thus, the configurational information inherent at the sp^3 center at C4a in **25** is forfeited at the stage of retro-Mannich intermediate **28**, en route to racemate **26**. Of course, exploitation of this mechanistic distinction requires that the reaction be conducted in the context of enantioenriched or ideally enantiopure starting material. In this way, one might hope to determine the degree of chirality transfer in the rearrangement step. With this goal in mind, L-tryptophan was used as the starting material to reach substrate (+)-**24** (Scheme 6) via the *P. coerulescens* co-metabolite coerulescine ((*S*)-**21**).[14] It was also possible to work out chromatographic procedures to separate the enantiomers of **24** on both analytical and

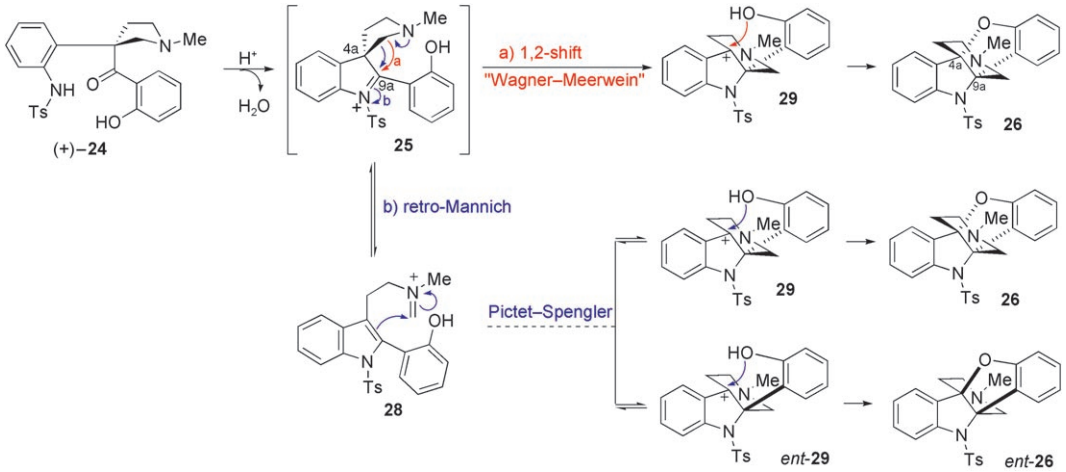


Scheme 6. Reagents and conditions: a) MeOH, 2 N aq HCl; b) 37% aq formaldehyde, MeOH, reflux; c) TMSCl, MeOH, reflux; d) 37% aq formaldehyde, $NaBH_3CN$, MeOH, AcOH, 69% after recrystallization (4 steps); e) NBS, AcOH, THF, 0°C, quant.; f) 7 M NH_3/MeOH, RT, quant.; g) TFA, Et_3N, CH_2Cl_2, quant.; h) $NaBH_4$, EtOH, reflux, 73%; i) LiHMDS, TsCl, THF, 98%; j) 1. *t*BuLi, THF, −78°C, 2. **32**, 83%; k) TFA, CH_2Cl_2, 85%. TMS = trimethylsilyl.

preparative scales.[15] Similarly, separation of the enantiomers of **26** could be accomplished on an analytical scale.[16] With these capabilities, it was possible to analyze the rearrangement step in considerable detail.

Substantially enantiopure (+)-**24** (>95% *ee*) was subjected to the now-standard rearrangement conditions. We initially planned to monitor the optical enrichment of **26** as a function of time. In the event, as soon as **26** was produced (as judged by HPLC) it emerged as the racemate.[16] On the basis of these findings, it is clear that the rearrangement of (+)-**24** to **26** occurs with loss of configurational information, presumably via **28**.

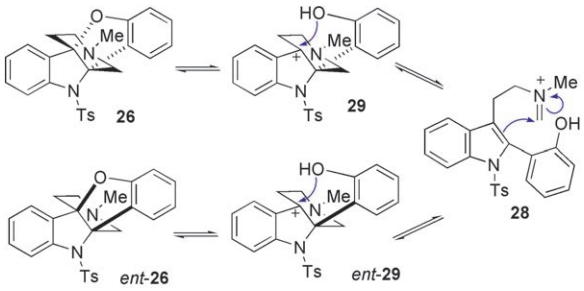
We also examined the optical purity of unconsumed **24** as the reaction proceeded. In the event, **24** was re-isolated and found to have fully retained its optical activity.[16] This observation can be readily explained through inspection of the proposed reaction pathway. Thus, the first step entails the cyclization of ketone **24** to indolenine **25** (Scheme 5). From there, the retro-Mannich reaction to give **28** abrogates the incident chirality and product **26** emerges as a racemate. These data do not tell us intrinsically whether achiral **28**, on its



Scheme 5. Possible mechanistic pathways of the rearrangement sequence.

formation, must progress on to **26** or whether it can revert to **25**. In principle, **28** and **25** could well be in equilibrium. All that can be said with confidence is that **28** does not revert all the way back to **24**, for it is **24** which was detected.[17] Given our inability to resolve this issue (that is, whether achiral **28** reverts to racemic **25**), there would remain an uncertainty as to whether the Pictet–Spengler pathway actually occurs. In principle, if **28** reverted to racemic **25**, a pathway to racemic **26** would be enabled even in the absence of a direct cyclization of **28** to *rac*-**26**.[18]

To further understand the pathway, it was also necessary to determine whether **26** itself racemizes spontaneously under the conditions of its formation. Since we were able to resolve **26** by HPLC,[16] we subjected optically pure compound to the reaction conditions. It was found that **26** did indeed racemize, but at a rate that would not have immediately generated racemate from the initial cyclization of **24** (Scheme 7).[19]



Scheme 7. Racemization of **26**.

In retrospect, the accessibility of substantially enantiomerically pure **24**, either through synthesis or through chromatographic resolution turned out to be quite valuable. In particular, it served to show the intervention of a mechanistically dominant intermediate and the reversibility of the key steps.

In the following Communication, we show how the chemistry elucidated above served us well in the context of the total synthesis of phalarine.[7]

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[1] N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, D. Gardner, R. I. Willing, *Phytochemistry* **1999**, *51*, 153.
[2] a) S. P. Marsden, K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.* **1994**, *116*, 11143; b) J. Schkeryantz, J. Woo, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 7025; c) K. M. Depew, S. J. Danishefsky, N. Rosen, L. Sepp-Lorenzino, *J. Am. Chem. Soc.* **1996**, *118*, 12463; d) S. D. Edmondson, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 1190; *Angew. Chem. Int. Ed.* **1998**, *37*, 1138.
[3] a) C. A. Bourke, S. M. Colegate, S. Slattery, N. Oram, *Aust. Vet. J.* **2003**, *81*, 635; b) N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, I. Vit, R. I. Willing, *Phytochemistry* **1998**, *48*, 437.
[4] C. Chan, C. Li, F. Zhang, S. J. Danishefsky, *Tetrahedron Lett.* **2006**, *47*, 4839–4841.
[5] a) B. Witkop, J. B. Patrick, *J. Am. Chem. Soc.* **1953**, *75*, 2572; b) A. W. Burgett, Q. Li, Q. Wei, P. G. Harran, *Angew. Chem.* **2003**, *115*, 5111; *Angew. Chem. Int. Ed.* **2003**, *42*, 4961.
[6] a) G. Buchi, R. E. Manning, S. A. Monti, *J. Am. Chem. Soc.* **1964**, *86*, 4631; b) G. Buchi, R. E. Manning, *J. Am. Chem. Soc.* **1966**, *88*, 2532.
[7] See the following Communication: C. Li, C. Chan, A. C. Heimann, S. J. Danishefsky, *Angew. Chem.* **2006**, DOI: 10.1002/ange.200604072; *Angew. Chem. Int. Ed.* **2006**, DOI: 10.1002/anie.200604072.
[8] a) E. E. van Tamelen, J. P. Yardley, M. Miyano, W. B. Hinshaw, *J. Am. Chem. Soc.* **1969**, *91*, 7333; b) S. D. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147.
[9] On migratory aptitudes, see: J. March, *Advanced Organic Chemistry*, Wiley, New York, **1992**, pp. 1058–1061.
[10] CCDC-620358 and 620502 contain the supplementary crystallographic data for compounds **24** and **27**, respectively. In addition we also provide a crystal structure of the 6-bromo derivative of compound **18** (CCDC-620357), which strongly suggests the rotameric state shown. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre: www.ccdc.cam.ac.uk/data request/cif.
[11] For an example, see: S. M. Starling, S. C. Vonwiller, J. N. H. Reek, *J. Org. Chem.* **1998**, *63*, 2262.
[12] For a proposed retro-Mannich reaction which led to epimerization of reserpine to isoreserpine, see: a) A. J. Gaskell, J. A. Joule, *Tetrahedron* **1967**, *23*, 4053; for an alternative mechanism for the reserpine epimerization, see: b) L. H. Zhang, A. K. Gupta, J. M. Cook, *J. Org. Chem.* **1989**, *54*, 4708.
[13] E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797.
[14] a) For the preparation of **31**, see: G. Palmisano, R. Annunziata, G. Papeo, M. Sisti, *Tetrahedron: Asymmetry* **1996**, *7*, 1; b) coerulescine: N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, I. Vit, R. I. Willing, *Phytochemistry* **1998**, *48*, 437.
[15] Preparative HPLC was performed on a Chiralcel OD-H column (250 × 20 mm), $\lambda = 280$ nm, hexane/2-propanol = 9/1, flow rate = 12.0 mL min^{-1}. $R_t = 11.3$ min (enantiomer **24A**), $R_t = 17.3$ min (**24B**).
[16] Analytical chiral HPLC was performed on a Chiralcel OD-H column (250 × 4.6 mm), $\lambda = 280$ nm, hexane/2-propanol = 19/1, flow rate = 1.2 mL min^{-1}. Under these conditions, a mixture of racemic **24** and **26** gave the following peaks which were assigned by MS: $R_t = 5.9$ (enantiomer **26A**), $R_t = 10.5$ min (**26B**), $R_t =$ 12.7 min (**24A**), R_t 16.3 min (**24B**).
[17] The recovery of **24** without loss of configurational integrity while **26** is immediately produced in racemic form serves to rule out another unlikely but potential sequence which would avoid the steps **24**→**25**. This route would have involved ring expansion of **24** to produce a tertiary alcohol. Cyclization of the phenolic hydroxy group to the migration origin followed by cyclization of the NH group to the tertiary alcohol would afford **26**, but without loss of configurational integrity.
[18] a) A. H. Jackson, A. E. Smith, *Tetrahedron* **1965**, *21*, 989; b) A. H. Jackson, A. E. Smith, *Tetrahedron* **1968**, *24*, 403; c) A. H. Jackson, P. Smith, *Tetrahedron* **1968**, *24*, 2227.
[19] The optically pure product racemized under the rearrangement conditions (4.5 μM in toluene, CSA (2 equiv), 130 °C) with a half life of 136 min. In contrast, the rearrangement reaction immediately produces racemate under these conditions. The half life in going from **24**→**26** was 40–55 min.

