Cycloaddition Hot Paper

Deutsche Ausgabe: DOI: 10.1002/ange.201505126
Internationale Ausgabe: DOI: 10.1002/anie.201505126

Pentafulvene for the Synthesis of Complex Natural Products: Total Syntheses of (±)-Pallambins A and B**

*Christian Ebner and Erick M. Carreira**

Abstract: *The first total syntheses of pallambins A and B are enabled by the use of pentafulvene in an unprecedented Diels–Alder reaction. After elaboration of the adduct through chemoselective cyclopropanation, strategic C–H insertion affords the dense tetracyclic core of the natural products. 1,3-Dipolar cycloaddition and palladium(II)-catalyzed alkoxycarbonylation were leveraged for the construction of the hexacyclic scaffold en route to both natural products.*

Liverworts (Marchantiophyta) are some of the most primitive plants and are widely distributed throughout the world. These bryophytes are a rich source of terpenoid natural products which possess intriguing carbon skeletons.[1] In 2012, two cyclopropane-containing diterpenoids, pallambin A (**1**) and pallambin B (**2**), were isolated from extracts of the liverwort *Pallavicinia ambigua* (Figure 1 a).[2] The structurally related pallambins C (**3**) and D (**4**) were also present in the extracts.[3]

1 and **2** possess unprecedented and highly congested tetracyclo[4.4.0^{3,5}.0^{2,8}]decane cores, which embed cyclopropanes in a hindered environment, and include double gauche pentane interactions with the C(10) methyl group. Additionally, these natural products comprise ten contiguous stereocenters, two of which are quaternary. Given these features, **1** and **2** constitute formidable challenges for total synthesis. Given our interest in the syntheses of complex fused ring systems,[4] we decided to embark on a synthetic endeavor towards these diterpenoids. Herein, we report the first total syntheses of the (±)-pallambins A (**1**) and B (**2**).

Strategic considerations led to the diene **6** as a starting point for a synthetic route (Scheme 1). We became intrigued by the possibility of preparing **6** in a single step by a Diels–Alder cycloaddition involving fulvene. There are three salient features to the study of a route commencing with fulvene. Firstly, unlike substituted cyclopentadienes, pentafulvene is not susceptible to isomerizations through thermally allowed 1,5-shifts. Secondly, the sp^2-hybridized bridge carbon atom enables a wide variety of transformations for its functionalization. Thirdly, the successful realization of the cycloaddition would constitute the first use of pentafulvene, the simplest

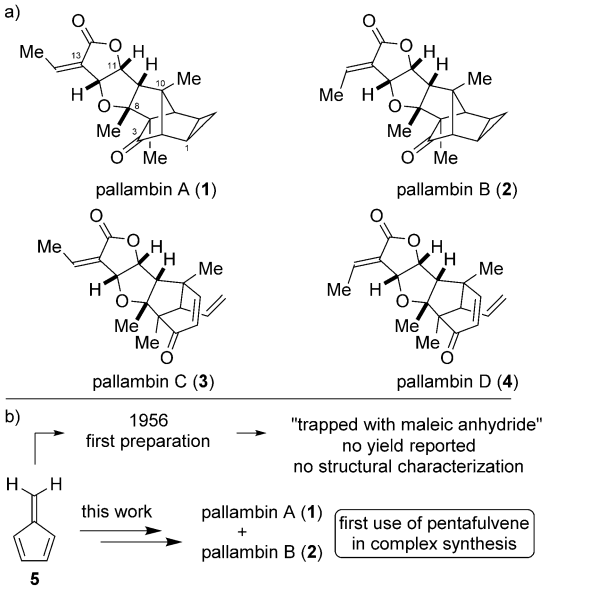
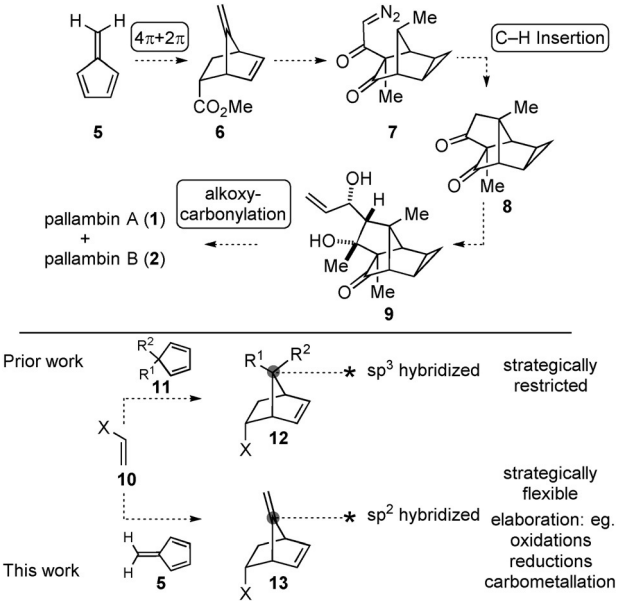


Figure 1. a) Structures of recently isolated pallambins A–D. b) First use of fulvene in complex molecule synthesis.



Scheme 1. Synthetic strategy towards pallambins A (**1**) and B (**2**).

[*] C. Ebner, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie, ETH Zürich, HCI H335
Vladimir-Prelog-Weg 3, 8093 Zürich (Switzerland)
E-mail: carreira@org.chem.ethz.ch
Homepage: http://www.carreira.ethz.ch

[**] We are grateful to Dr. N. Trapp and M. Solar for X-ray crystallographic analysis, and to Dr. M.-O. Ebert, R. Arnold, R. Frankenstein, and P. Zumbrunnen for NMR measurements. C.E. acknowledges the Stipendienfonds Schweizerische Chemische Industrie (SSCI).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201505126.

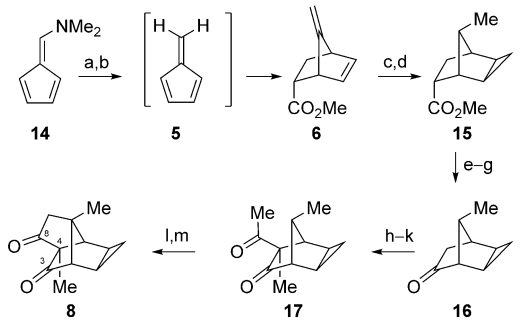
fulvene, in the context of complex natural product synthesis (Figure 1b).[5]

An important consideration in any synthetic approach to **1** and **2** is the construction of the sterically encumbered cyclopropane (Scheme 1). We surmised that its installation would have to precede the introduction of the C(10) quaternary center, as the attendant methyl group would preclude exo-cyclopropanation. Therefore, it was concluded that the cyclopropane would have to be installed early on, after the cycloaddition of fulvene. However, at the outset of the investigation the question of chemoselectivity (endocyclic vs. exocyclic olefin) was of concern because of the lack of literature precedence. A carbenoid C–H insertion reaction of **7** was envisioned for the construction of the quaternary center at C(10). Finally, late-stage alkoxycarbonylation of **9** would generate both the tetrahydrofuran and the γ-lactone of **1** and **2** in one step.

Fulvene, an isomer of benzene, is known to undergo facile light- or heat-induced polymerizations.[6] Additionally, this highly reactive hydrocarbon was found to be acid- and base-sensitive, and stable in neat form only below −70 °C. Therefore, our first objective was to identify a reactive dienophile which could serve as a ketene equivalent and outcompete polymerization reactions of fulvene. The starting point of our investigation was inspired by a report by Trost and co-workers describing the small-scale use of fulvene in hetero-Diels–Alder reactions with dialkylazodicarboxylates.[7] In this work, fulvene was generated by reduction and Hofmann elimination of bench-stable dimethylaminofulvene. After extensive experimentation, we found that fulvene could smoothly be generated in this manner in methyl acrylate (Scheme 2). Upon addition of Et_2AlCl, the desired cycloadduct **6** was isolated in 62% yield on large scale (> 25 g).

We then explored the challenging introduction of the cyclopropane motif. Substantial experimentation was necessary to identify reaction conditions that led to reaction of the endocyclic olefin and the desired exo selectivity. Established cyclopropanation protocols such as $ZnEt_2/CH_2I_2$,[8a] $ZnEt_2/CH_2I_2/F_3CCO_2H$,[8b] $ZnEt_2/CH_2I_2/(n\text{BuO})_2P(O)OH$,[8c] and $i\text{Bu}_3\text{Al}/CH_2I_2$[8d] suffered from low conversion and poor chemoselectivity. In contrast, when **6** was subjected to Denmark's conditions ($ZnEt_2/ClCH_2I$), the desired cyclopropane was isolated as a single diastereomer in 85% yield (Scheme 2).[8e] The remaining exocyclic olefin was hydrogenated in the presence of Wilkinson's catalyst in 96% yield, thus providing **15** as a single diastereomer. The remarkable selectivity presumably arises from steric shielding of the *Si*-face of the double bond by the cyclopropane. Next, we turned our attention to the generation of the C(3) ketone and the quaternary center at C(4). While direct attempts to convert **15** into **16** were met with failure,[9] a sequence of α-hydroxylation with molecular oxygen, reduction, and diol cleavage provided a high yielding alternative to this end (82%).

Generation of the lithium enolate of **16** and trapping with excess methyl iodide gave the corresponding methylated ketone in 89% yield (Scheme 2). Attempts to prepare the 1,3-diketone **17** from the corresponding enolate or silylenol ether revealed its profound lack of reactivity towards acylation. Consequently, a two-step procedure was performed using the more reactive acetaldehyde as electrophile. After generation of the TBS-enol ether, Mukaiyama aldol reaction with acetaldehyde in the presence of $BF_3{\cdot}OEt_2$ yielded a mixture of two epimeric alcohols. These β-hydroxy ketones proved to be unstable because of their propensity to undergo a retro-aldol reaction. When Dess–Martin periodinane was employed, long reaction times and considerable amounts of the retroaldol product were observed. We reasoned that the Lewis-acidic nature of the reagent might lead to a competition scenario between oxidation and retro-aldol reaction. Therefore, Dess–Martin periodinane was first mixed with equimolar amounts of *t*BuOH, a procedure known to increase the rate of oxidation.[10] Indeed, applying this protocol led to exclusive formation of **17**.

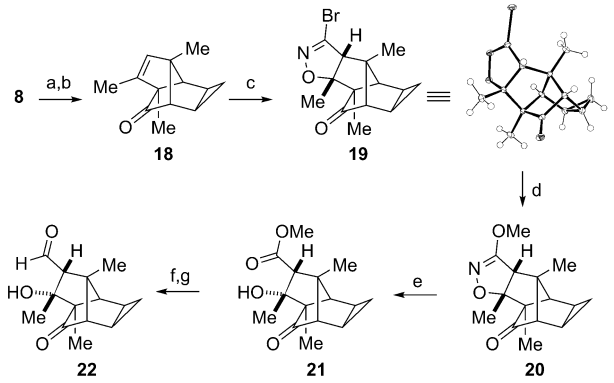


Scheme 2. Reagents and conditions: a) $LiAlH_4$ (1.0 equiv), Et_2O, −17 °C, 88%; b) methyl acrylate, MeI (1.0 equiv), 0 °C; then Et_2AlCl (0.3 equiv), −20 °C to 5 °C, 62%, d.r. = 10:1; c) $ZnEt_2$ (2.0 equiv), $ClCH_2I$ (4.0 equiv), CH_2Cl_2, 0 °C, 85%, d.r. > 20:1; d) $[RhCl(PPh_3)_3]$ (4.0 mol%), H_2 (1 atm), CH_2Cl_2, RT, 96%, d.r. > 20:1; e) $i\text{Pr}_2\text{NLi}$ (2.0 equiv), THF, −78 °C; then $P(OEt)_3$ (1.0 equiv), DMPU (1.0 equiv), O_2 (bubbling), −90 °C, 85%, d.r. = 10:1; f) $LiAlH_4$ (0.7 equiv), Et_2O, 0 °C; g) $NaIO_4$ (1.5 equiv), THF/phosphate buffer (aq, pH 7) (1:1), 0 °C, 97% over 2 steps; h) $i\text{Pr}_2\text{NLi}$ (2.5 equiv), THF, −78 °C to 0 °C; then MeI (18 equiv); then NEt_3 (18 equiv), 89%, d.r. = 5:1; i) TBSOTf (1.03 equiv), NEt_3 (1.5 equiv), CH_2Cl_2, 0 °C; j) MeCHO (10.0 equiv), $BF_3{\cdot}OEt_2$ (2.0 equiv), CH_2Cl_2, −90 °C; 3 × recycled; k) DMP (2.0 equiv), *t*BuOH (2.0 equiv), CH_2Cl_2, 0 °C, 70% over 3 steps; l) $LiN(SiMe_3)_2$ (1.15 equiv), −78 °C; then $F_3CCH_2O_2CCF_3$ (1.3 equiv); then NEt_3 (1.5 equiv), MsN_3 (1.5 equiv), MeCN, RT; m) $[Rh_2(OAc)_4]$ (1.0 mol%), CH_2Cl_2, reflux, 76% from **17**. DMP = Dess–Martin periodinane, DMPU = 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one, Ms = methanesulfonyl, THF = tetrahydrofuran, TBS = *tert*-butyldimethylsilyl. Tf = trifluoromethanesulfonyl.

With access to **17**, we established the crucial C–H insertion step for completion of the tetracyclo[$4.4.0^{3,5}.0^{2,8}$]decane core (Scheme 2). Thus, **17** was exposed to the diazo transfer conditions reported by Danheiser et al.[11] Since the diazo compound proved to be unstable towards silica gel, the unpurified material was directly treated with catalytic amounts of $[Rh_2(OAc)_4]$. Gratifyingly, the desired product **8** was isolated in 76% overall yield, thereby completing the core structure of **1** and **2**.

The challenge to stereoselectively introduce the C(8) methyl group was tackled next. Addition of organometallic reagents to the C(8) ketone was considered futile since the essential *Si*-face attack was anticipated to be hampered by the considerable steric shielding of the norbornene system. The decision was made to rely on this bias for the stereoselective

introduction of the C(8) alcohol and simultaneously functionalize the C(9) position by a cycloaddition reaction. For this purpose, ketone **8** was transformed into the corresponding enol triflate and then exposed to Negishi cross-coupling conditions with $ZnMe_2$ to give **18** in 64% overall yield (Scheme 3). The newly formed trisubstituted olefin **18**

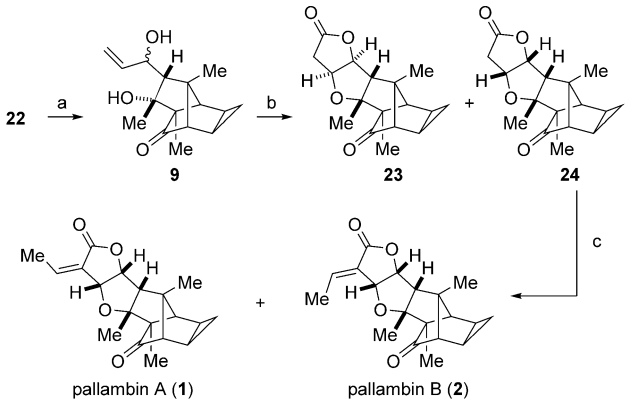


Scheme 3. Reagents and conditions: a) iPr_2NLi (1.5 equiv), THF, −78 °C, then $PhNTf_2$ (2.0 equiv), −78 °C to 5 °C, 64%; b) $[Pd(PPh_3)_4]$ (5 mol%), $ZnMe_2$ (5.0 equiv), THF, 0 °C to RT, quant; c) Br_2CNOH (2.5 equiv), $KHCO_3$ (5.0 equiv), EtOAc, RT, 91%; d) LiOMe (20 equiv), MeOH, reflux, 94%; e) $B(OH)_3$ (6.0 equiv), Ra-Ni (1.0 equiv), H_2 (1 atm), $MeOH/H_2O$ (5:1), RT, 91%; f) iBu_2AlH (3.0 equiv), *n*BuLi (3.0 equiv), THF, 0 °C, then **21**, THF, −60 °C to 0 °C, 89%; g) $(COCl)_2$ (1.6 equiv), DMSO (2.7 equiv), NEt_3 (5.0 equiv), CH_2Cl_2, −78 °C to RT, quant. DMSO = dimethylsulfoxide. For ORTEP representation the thermal ellipsoids are shown at 50% probability.

smoothly underwent 1,3-dipolar cycloaddition with bromonitrile oxide, generated in situ from dibromoformaldoxime and $KHCO_3$, thus providing the isoxazoline **19** in 91% yield.[12] Compound **19** was obtained as a single regio- and diastereoisomer. Recrystallization provided crystals suitable for X-ray diffractometry, thereby unambiguously confirming the relative stereochemical assignment.

Methods for functionalizing bromoisoxazolines are rare. Most commonly, they are converted into β-hydroxy nitriles using either TMSCl/NaI[13a] or NaSEt[13b] or reduced to β-hydroxy amines. After extensive experimentation, including transition-metal-catalyzed couplings, radical dehalogenations, or substitution reactions with vinyl anions, no effective functionalization of **19** could be established. Additionally, when **19** was converted into the corresponding β-hydroxy nitrile using TMSCl/NaI, reduction to the aldehyde was found to be exceedingly difficult under a variety of conditions (iBu_2AlH, $iBu_2AlH{\cdot}SMe_2$,[14a] Red-Al, $Li(iBu)_2(nBu)AlH$,[14b] Ra-Ni/NaH_2PO_2[14c] or Ra-Ni/formic acid[14d]) and alternative approaches were deemed necessary. Thus, bromide–methoxide exchange,[15] followed by Ra-Ni-mediated hydrogenolysis of the N–O bond smoothly provided ester **21** in 91% overall yield (Scheme 3). While ester reduction with iBu_2AlH led to decomposition of both starting material and product, the use of non-Lewis-acidic $Li(iBu)_2(nBu)AlH$ (generated from iBu_2AlH and *n*BuLi)[16] cleanly provided the corresponding diol in 89% yield. Subsequent Swern oxidation gave aldehyde **22** in excellent yield.

The remaining challenge of introducing the tetrahydrofuran and the γ-lactone was met next. The pioneering work of Semmelhack and co-workers on palladium(II)-mediated alkoxycarbonylation emerged as an appealing method to simultaneously generate the remaining two rings.[17] Addition of the vinylcerium reagent to **22** gave allylic alcohol **9** in 90% yield (d.r. = 60:40; Scheme 4).[18] Since attempts to separate



Scheme 4. Reagents and conditions: a) $CeCl_3$ (3.0 equiv), vinylmagnesium bromide (3.0 equiv), THF, −78 °C, then **22**, −78 °C to RT, 90%, d.r. = 60:40; b) $Pd(OAc)_2$ (10 mol%), TMTU (10 mol%), NH_4OAc (10 mol%), $CuCl_2$ (2.5 equiv), propylene oxide (5.0 equiv), CO (1 atm), THF, 50 °C, 55% for **24**, 26% for **23**; c) 1. iPr_2NLi (1.4 equiv), THF, −78 °C, then MeCHO (5.7 equiv), THF, −78 °C to −40 °C; 2. NEt_3 (15 equiv), DMAP (cat.), MsCl (5.0 equiv), CH_2Cl_2, RT, 87% (pallambin B), 11% (pallambin A). DMAP = 4-(*N*,*N*-dimethylamino)pyridine, TMTU = tetramethylthiourea.

the two diastereomers at this stage were unsuccessful, the mixture was directly employed in the subsequent cyclization step. When **9** was reacted under conditions optimized by Yang and co-workers,[19] using 10 mol% $Pd(OAc)_2$ and $CuCl_2$ as the oxidant, the desired diastereomer **24** was obtained in 55% yield (83% based on the correct diastereomer) along with 26% of isomer **23**. Having successfully obtained the hexacyclic system of the natural products, the only remaining task was the installation of the ethylidene group. While attempts to generate the corresponding β-phosphonate[20] and subsequent Horner–Wadsworth–Emmons olefination with acetaldehyde[21] failed, a two-step aldol condensation provided a mixture of **1** and **2**. The natural products could be separated by preparative thin-layer chromatography to give pallambin B (**2**) in 87% yield and pallambin A (**1**) in 11% yield. The spectral data were in excellent agreement with those in the isolation report.

In conclusion, we have described the first total syntheses of (±)-pallambins A (**1**) and B (**2**). The synthetic strategy is centered around the use of fulvene as diene in a Diels–Alder reaction early in the synthesis. Additional salient features of the route include a highly chemo- and diastereoselective cyclopropanation as well as a strategic C–H insertion to establish the tetracyclic core of the natural products. Furthermore, a 1,3-dipolar cycloaddition and a palladium(II)-catalyzed alkoxycarbonylation allowed the efficient elaboration of the congested scaffold. Efforts to expand the use of

the fulvene Diels–Alder reaction to other targets are the subject of ongoing research in our laboratory and will be reported in due course.

Keywords: C–H insertion · cycloaddition · natural products · small-ring systems · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11227–11230
Angew. Chem. **2015**, *127*, 11379–11382

[1] Y. Asakawa in *Progress in the Chemistry of Organic Natural Products* (Eds.: W. Herz, H. Grisebach, G. W. Kirby), Springer, Vienna, **1982**, pp. 1–285.
[2] L.-N. Wang, J.-Z. Zhang, X. Li, X.-N. Wang, C.-F. Xie, J.-C. Zhou, H.-X. Lou, *Org. Lett.* **2012**, *14*, 1102–1105.
[3] For recent total syntheses of pallambins C and D, see: X.-S. Xu, Z.-W. Li, Y.-J. Zhang, X.-S. Peng, H. N. C. Wong, *Chem. Commun.* **2012**, *48*, 8517–8519.
[4] For recent total syntheses of highly congested natural products from our laboratory, see: a) C. S. Schindler, L. Bertschi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9229–9232; *Angew. Chem.* **2010**, *122*, 9415–9418; b) M. E. Weiss, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 11501–11505; *Angew. Chem.* **2011**, *123*, 11703–11707; c) O. F. Jeker, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3474–3477; *Angew. Chem.* **2012**, *124*, 3531–3534; d) N. Huwyler, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 13066–13069; *Angew. Chem.* **2012**, *124*, 13243–13246; e) S. Diethelm, E. M. Carreira, *J. Am. Chem. Soc.* **2013**, *135*, 8500–8503; f) S. Breitler, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 11168–11171; *Angew. Chem.* **2013**, *125*, 11375–11379; g) S. A. Ruider, T. Sandmeier, E. M. Carreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 2378–2382; *Angew. Chem.* **2015**, *127*, 2408–2412.
[5] For the trapping of fulvene with maleic anhydride, see: J. Thiec, J. Wiemann, *Bull. Soc. Chim. Fr.* **1956**, 177–180.
[6] D. Meuche, M. Neuenschwander, H. Schaltegger, H. U. Schlunegger, *Helv. Chim. Acta* **1964**, *47*, 1211–1215.
[7] B. M. Trost, R. M. Cory, *J. Org. Chem.* **1972**, *37*, 1106–1110.
[8] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53–58; b) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie, Y. Shi, *J. Org. Chem.* **2004**, *69*, 327–334; c) A. Voituriez, L. E. Zimmer, A. B. Charette, *J. Org. Chem.* **2010**, *75*, 1244–1250; d) K. Maruoka, Y. Fukutani, H. Yamamoto, *J. Org. Chem.* **1985**, *50*, 4412–4414; e) S. E. Denmark, J. P. Edwards, *J. Org. Chem.* **1991**, *56*, 6974–6981.
[9] a) P. Li, J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535; b) B. M. Trost, Y. Tamaru, *J. Am. Chem. Soc.* **1975**, *97*, 3528–3530.
[10] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; for an excellent overview, see: M. Fernandez, G. Tojo in *Oxidation of Alcohols and Ketones: A Guide to Current Common Practice* (Ed.: E. Tojo), Springer, New York, **2006**, p. 194.
[11] R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959–1964.
[12] a) I. DePaolini, *Gazz. Chim. Ital.* **1930**, *60*, 700–704; for its preparation and use in total synthesis, see: b) D. M. Vyas, Y. Chiang, T. W. Doyle, *Tetrahedron Lett.* **1984**, *25*, 487–490; c) T. J. Maimone, J. Shi, S. Ashida, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 17066–17067.
[13] a) M. G. Kociolek, K. P. Kalbarczyk, *Synth. Commun.* **2004**, *34*, 4387–4394; b) M. H. Seo, Y. Y. Lee, Y. M. Goo, *Synth. Commun.* **1994**, *24*, 1433–1439.
[14] a) J. S. Cha, O. O. Kwon, M. K. Jeoung, E. J. Kim, *Bull. Korean Chem. Soc.* **1994**, *15*, 1021–1023; b) T. Ritter, P. Zarotti, E. M. Carreira, *Org. Lett.* **2004**, *6*, 4371–4374; c) O. G. Backeberg, B. Staskun, *J. Chem. Soc.* **1962**, 3961–3963; d) B. Staskun, O. G. Backeberg, *J. Chem. Soc.* **1964**, 5880–5881.
[15] P. Caldirola, M. Ciancaglione, M. De Amici, C. De Micheli, *Tetrahedron Lett.* **1986**, *27*, 4647–4650.
[16] S. Kim, K. H. Ahn, *J. Org. Chem.* **1984**, *49*, 1717–1724.
[17] M. F. Semmelhack, C. Bodurow, M. Baum, *Tetrahedron Lett.* **1984**, *25*, 3171–3174.
[18] Prior chelation with Bu_2BOTf resulted in an increased d.r. of 6:1, but provided the product in substantial lower yield (18%).
[19] a) Z. Li, Y. Gao, Y. Tang, M. Dai, G. Wang, Z. Wang, Z. Yang, *Org. Lett.* **2008**, *10*, 3017–3020; b) Z. Li, Y. Gao, Z. Jiao, N. Wu, D. Z. Wang, Z. Yang, *Org. Lett.* **2008**, *10*, 5163–5166; for the use of this transformation during the total synthesis of pallambin C and D, see Ref. [3].
[20] J. A. Jackson, G. B. Hammond, D. F. Wiemer, *J. Org. Chem.* **1989**, *54*, 4750–4754.
[21] J. S. Yu, D. F. Wiemer, *J. Org. Chem.* **2007**, *72*, 6263–6265.

Received: June 5, 2015
Published online: July 31, 2015