

The Catalytic Enantioselective Total Synthesis of (+)-Liphagal**

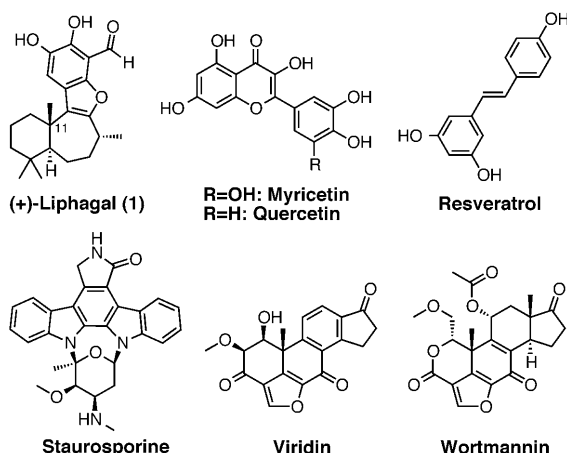
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The tetracyclic meroterpenoid natural product (+)-liphagal (**1**) was isolated in 2006 by Andersen and co-workers from the Caribbean sponge *Aka coralliphaga*,^[1] and is one of a number of natural product inhibitors of phosphatidylinositol 3-kinase (PI3K). Other natural product inhibitors include myricetin, quercetin, resveratrol, staurosporine, viridin, and wortmannin (Scheme 1).^[2] The PI3K family of enzymes participates in the

cancer.^[3] The inhibitory activity of liphagal is noteworthy because of its selective inhibition of PI3K α , a lipid kinase isoform that holds a central role in several cancers.^[4] In this context, liphagal was found to have an IC_{50} value of 100 nM against PI3K α and was tenfold more potent against isoform α than γ . In addition, liphagal is cytotoxic toward LoVo (human colon), CaCo (human colon), and MDA-468 (human breast) tumor cell lines, with IC_{50} values of 0.58, 0.67, and 1.58 μ M, respectively.^[1]

From a structural perspective, liphagal possesses an unprecedented [6-7-5-6] tetracyclic skeleton, and has attracted significant attention from the synthetic organic community. The isolation and structure determination was reported concomitantly with the first total synthesis of (\pm)-**1** through a biomimetic strategy.^[1,5] Subsequently, Andersen and co-workers determined the absolute configuration,^[6] which was corroborated by other research groups through formal and total syntheses.^[7-9] We became interested in both the potent biological activity and the complex tetracyclic structure of liphagal, as highlighted by the chiral quaternary carbon center at C(11). Herein we report the first catalytic enantioselective total synthesis of (+)-liphagal.

Retrosynthetically, we envisioned simplification of the aromatic ring of liphagal to dimethoxybenzofuran **2**, a known precursor to the natural product (Scheme 2).^[7] Disconnection of the tetracycle along the benzofuran moiety led back to α -bromoaryl dienone **3**. Reduction of the sterically hindered trisubstituted olefin to establish the *trans* ring fusion was seen as a major challenge. The α -bromoaryl dienone **3** could arise from a ring expansion of strained cyclobutene **4**. Excision of the cyclobutene and α -aryl group from ketone **4** revealed chiral cyclopentenone (*R*)-**5**. The enantiomeric enone (*S*)-**5**^[10] was previously prepared from achiral enol carbonate **6**^[11a] as part of our ongoing research program aimed at the stereose-



Scheme 1. Natural product inhibitors of PI3K.

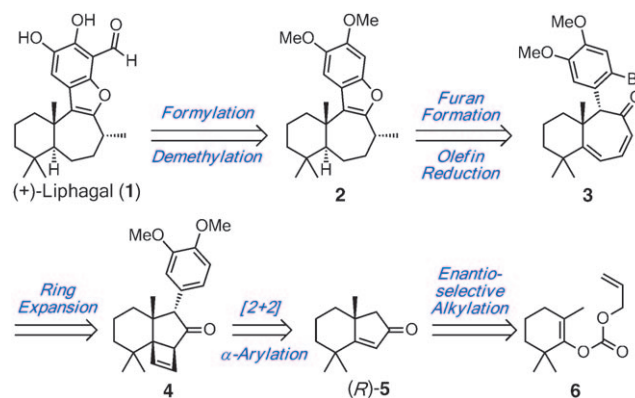
regulation of numerous biological functions and has been directly implicated in the pathogenesis of diabetes and

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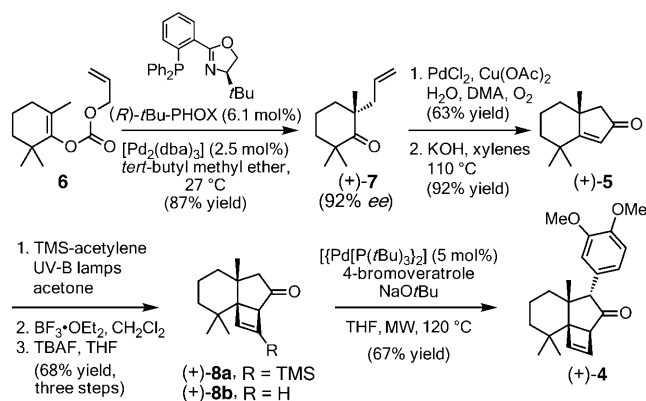
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Scheme 2. Retrosynthesis of liphagal.

lective synthesis of natural products containing quaternary carbon centers.^[11,12] To this end, we have reported a series of palladium-catalyzed enantioselective decarboxylative alkylation reactions that employ the *t*Bu-PHOX ligand scaffold in conjunction with allyl enol carbonates, silyl enol ethers, and racemic β -ketoesters to produce a wide array of α -quaternary substituted ketones.^[11–14] With this general strategy in mind, we initiated efforts toward a total synthesis of (+)-liphagal.

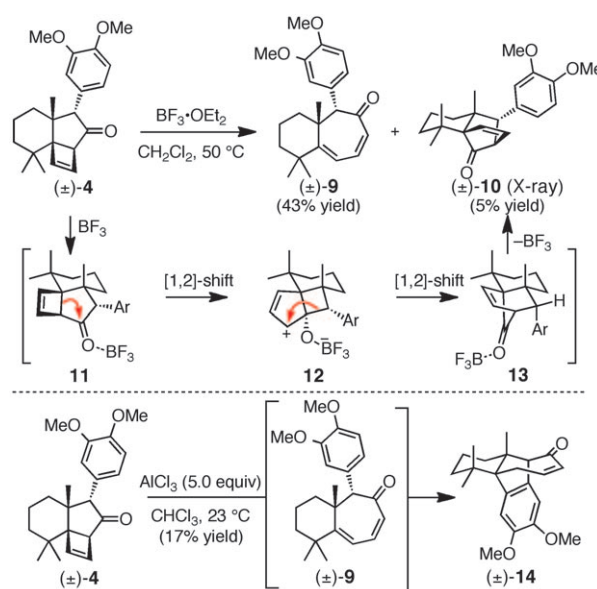
The forward synthesis commenced with a palladium-catalyzed decarboxylative alkylation of enol carbonate **6** to furnish tetrasubstituted ketone **7** in 87% yield and 92% *ee* (Scheme 3).^[11,15] This intermediate was elaborated to bicycle



Scheme 3. Catalytic enantioselective preparation of synthetic building block (+)-7 and chemical elaboration to (+)-4. dba = *trans,trans*-dibenzylideneacetone, DMA = *N,N*-dimethylacetamide, MW = microwave, TBAF = tetrabutylammonium fluoride, TMS = trimethylsilyl.

5 following our previously reported two-step sequence.^[10] The synthesis continued with exposure of enone **5** to trimethylsilylacetylene under UV irradiation, which promoted a [2+2] photocycloaddition.^[16] Exposure of the crude reaction mixture to BF₃·OEt₂ resulted in the formation of a single silylated cyclobutene product (**8a**).^[17] Subsequent removal of the trimethylsilyl group with TBAF yielded the chromatographically stable and pleasantly fragrant cyclobutene **8b**, a compound that contains three contiguous quaternary centers within the strained carbon framework.^[18,19] A microwave-assisted palladium-catalyzed α -arylation with 4-bromoveratrole installed the electron-rich aromatic moiety, thereby producing aryl ketone **4** as a single diastereomer.^[20,21]

At this stage in our synthesis, a Lewis acid mediated ring expansion by selective cleavage of strained cyclobutene **4** was attempted (Scheme 4). Exposure of tricyclic ketone **4** to BF₃·OEt₂ at 50 °C provided the desired cycloheptadienone product **9** in modest yield. Serendipitously, this compound was isolated alongside a crystalline by-product (**10**), which was suitable for X-ray diffraction analysis and structure determination.^[22] Bridged polycyclic ketone **10** is presumably the result of a Cargill rearrangement, which proceeds through two concerted [1,2]-carbon–carbon bond migrations.^[23] More specifically, activation of ketone **4** with BF₃ (to give **11**) promotes carbon-bond migration to rupture the cyclobutene and produce an allylic carbocation intermediate (**12**). The

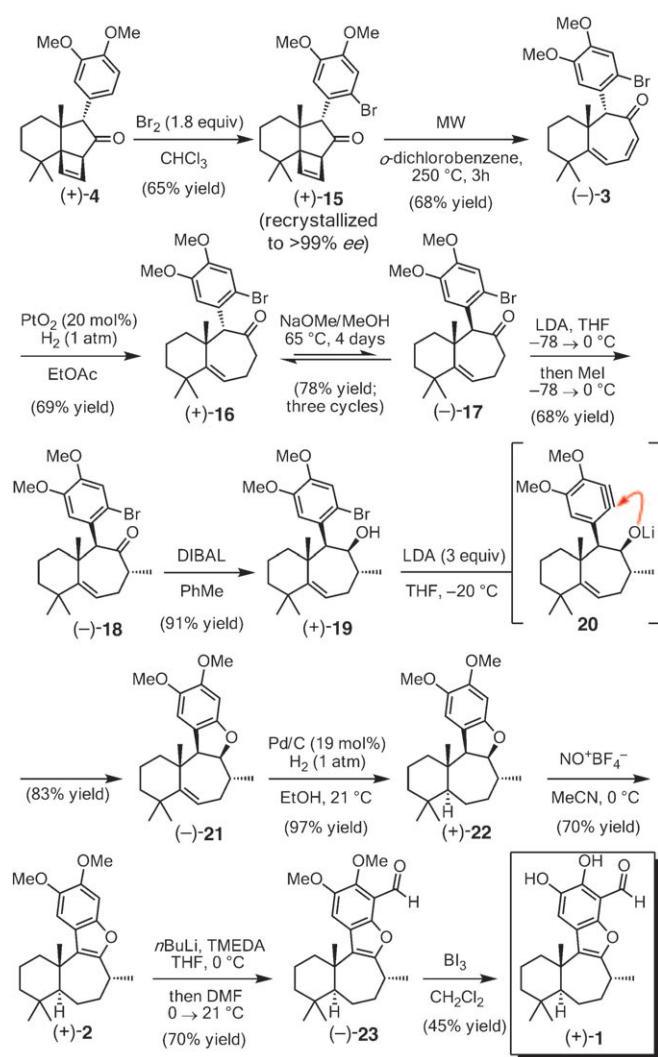


Scheme 4. Unexpected rearrangement and reactivity of strained cyclobutene **4**.

second carbon-bond migration forms a [2.2.1] bridged bicyclic core of Lewis acid complex **13**. Finally, loss of BF₃ generates the isolated product (**10**). Importantly, the stereospecific rearrangement mechanism allowed assignment of the relative configuration of cyclobutenes **8** from the unequivocal assignment of bridged bicycle **10**. In addition to BF₃·OEt₂, we discovered that AlCl₃ also promotes ring expansion of aryl cyclobutene **4** without formation of Cargill product **10**. However, under these reaction conditions we were intrigued to find a new side product, enone **14**, which arises from intramolecular 1,6-addition of the electron-rich arene fragment of **9** to the cycloheptadienone system. This result suggests that the arene resides in proximity to the trisubstituted olefin and also indicated that the aromatic moiety should be deactivated before ring expansion to avoid formation of **14**.

With this in mind, we sought to install a functional group handle on the aromatic ring that could be utilized for eventual formation of the benzofuran unit and could serve to deactivate the aromatic residue of **9** toward unwanted Friedel–Crafts reactions. We were impressed to find that chemoselective aromatic bromination occurred in the presence of the strained cyclobutene to furnish bromoarene **15** (Scheme 5). At this stage, crystallization of the crude product increased the enantiomeric excess to >99%. With the deactivated aromatic ketone in hand, we were pleased to find that treatment of bromide **15** with AlCl₃ furnished much improved yields of the corresponding ring-expanded product **3**. An optimized ring expansion from the [6-5-4] system to the desired [6-7] core (**3**) was accomplished in the absence of a Lewis acid by using microwave heating at 250 °C in *o*-dichlorobenzene.^[24] Chemoselective reduction of dienone **3** with Adams catalyst in ethyl acetate furnished ketone **16**, leaving the aromatic halide intact.

With the core carbon framework of liphagal (**1**) secured, our focus turned to the challenging stereoselective hydro-



Scheme 5. Completion of the total synthesis of liphagal (+)-1. DIBAL = diisobutylaluminum hydride, LDA = lithium diisopropylamide, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

genation of the trisubstituted olefin to establish the desired [6-7] *trans* ring fusion.^[25] Our strategy to effect this transformation was guided by our previous isolation of 1,6-addition product **14**, which provided evidence that hydrogenation to form a *trans* ring fusion would be sterically demanding (see above). To alleviate steric congestion, we proceeded with epimerization of the aryl substituent to form the β -oriented α -aryl ketone **17**. The mass recovery for this equilibration averaged 97%, and a 78% overall yield of **17** was obtained after three cycles of equilibration ($K_{eq(av)} = 0.76$).^[25] With the arene substituent further away from the trisubstituted olefin, we planned to rigidify the polycyclic system through formation of the fourth ring. This began with a diastereoselective methylation, which afforded the desired α -methyl cycloheptenone **18** in 68% yield.^[26] Reduction of this hindered ketone with DIBAL produced alcohol **19**, a substrate poised for the formation of the dihydrobenzofuran system. Initial attempts to form dihydrobenzofuran **21** were unsuccessful^[27] and prompted an unconventional strategy to accomplish the desired transformation. Gratifyingly, forma-

tion of dihydrobenzofuran **21** was accomplished by exposure of bromoarene **19** to LDA, with the reaction proceeding through the putative aryne intermediate **20**.^[28] This powerful aryne capture/cyclization strategy generated the highly congested dihydrobenzofuran product in 83% yield. With tetracycle **21** in hand, we set out to test the key stereoselective hydrogenation of the trisubstituted olefin. To our delight, we were able to isolate saturated homodecalin **22** in 97% yield by using catalytic Pd/C in ethanol under 1 atm H₂, with exclusive formation of the [6-7] *trans* ring fusion.

Having executed the synthesis of the challenging *trans* fused system, the completion of (+)-liphagal required three additional transformations: 1) construction of the benzofuran moiety, 2) installation of an aldehyde group, and 3) demethylation, the final two of which were known from previous syntheses.^[1,7] Oxidation of dihydrobenzofuran **22** to benzofuran **2** proved surprisingly difficult, and a tendency for over-oxidation was observed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).^[29] Upon switching to nitrosonium tetrafluoroborate, which oxidizes by hydride abstraction, dehydrogenation occurred in 70% yield to give benzofuran **2**.^[30] Aryl lithiation with *n*BuLi-TMEDA and quenching with anhydrous DMF installed the aldehyde functional group in **23**.^[7] This was followed by demethylation using boron triiodide to generate (+)-liphagal (**1**), which was identical in all respects to data reported in the literature.^[1]

In summary, we have successfully completed the first catalytic enantioselective total synthesis of (+)-liphagal (**1**) in 15 steps from known compounds (19 steps from commercially available materials). By applying a combination of catalytic enantioselective alkylation (**6**→**7**), two-carbon ring expansion via cyclobutene **15**, and an intramolecular aryne cyclization (**19**→**20**→**21**) we were able to access the tetracyclic core of the natural product in an enantioenriched form. Judicious choice of tetracyclic hydrogenation substrate **21** established the critical *trans*-[6-7] ring fusion and enabled completion of the total synthesis.

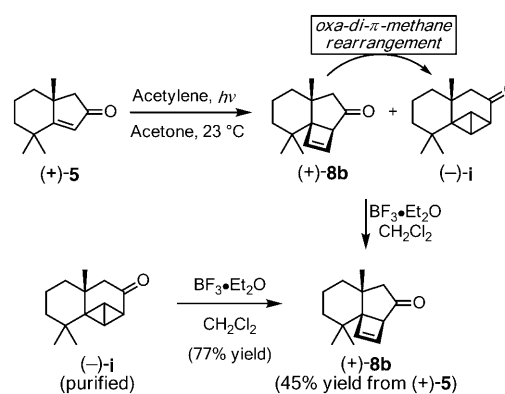
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- [1] F. Marion, D. E. Williams, B. O. Patrick, I. Hollander, R. Mallon, S. C. Kim, D. M. Roll, L. Feldberg, R. van Soest, R. J. Andersen, *Org. Lett.* **2006**, 8, 321–324.
- [2] T. J. Sundstrom, A. C. Anderson, D. L. Wright, *Org. Biomol. Chem.* **2009**, 7, 840–850.
- [3] a) L. C. Cantley, *Science* **2002**, 296, 1655–1657; b) J. A. Engelman, J. Luo, L. C. Cantley, *Nat. Rev. Genet.* **2006**, 7, 606–619; c) S. G. Ward, P. Finan, *Curr. Opin. Pharmacol.* **2003**, 3, 426–434; d) S. Ward, Y. Sotsios, J. Dowden, I. Bruce, P. Finan, *Chem. Biol.* **2003**, 10, 207–213; e) see Ref. [2].
- [4] Y. Samuels, Z. Wang, A. Bardelli, N. Silliman, J. Ptak, S. Szabo, H. Yan, A. Gazdar, S. M. Powell, G. J. Riggins, J. K. V. Willson, S. Markowitz, K. W. Kinzler, B. Vogelstein, V. E. Velculescu, *Science* **2004**, 304, 554, and references therein.

- [5] For a recent biomimetic formal synthesis of (\pm)-liphagal, see G. Mehta, N. S. Likhite, C. S. A. Kumar, *Tetrahedron Lett.* **2009**, *50*, 5260–5262.
- [6] a) R. Andersen, I. Hollander, D. M. Roll, S. C. Kim, R. G. Mallon, D. E. Williams, F. Marion, Fr Patent WO2006081659, **2006**; b) A. R. Pereira, W. K. Strangman, F. Marion, L. Feldberg, D. Roll, R. Mallon, I. Hollander, R. J. Andersen, *J. Med. Chem.* **2010**, *53*, 8523–8533.
- [7] J. H. George, J. E. Baldwin, R. M. Adlington, *Org. Lett.* **2010**, *12*, 2394–2397.
- [8] E. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, M. J. Cano, A. Haidour, R. Alvarez-Manzaneda, *Org. Lett.* **2010**, *12*, 4450–4453.
- [9] For additional studies directed toward the total synthesis of liphagal, see a) V. Deore, M. K. Lohar, R. Mundada, A. Roychowdhury, R. Vishwakarma, S. Kumar, *Synth. Commun.* **2011**, *41*, 177–183; b) Y. Zhang, E. Z. Oblak, E. S. D. Bolstad, A. C. Anderson, J. P. Jasinski, R. J. Butcher, D. L. Wright, *Tetrahedron Lett.* **2010**, *51*, 6120–6122.
- [10] R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.
- [11] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, *117*, 7084–7087; *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; c) J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz, W. A. Goddard III, *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877; d) M. Seto, J. L. Roizen, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 6979–6982; *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6876; e) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Org. Synth.* **2009**, *86*, 194–211; f) N. H. Sherden, D. C. Behenna, S. C. Virgil, B. M. Stoltz, *Angew. Chem.* **2009**, *121*, 6972–6975; *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843; g) J. Streuff, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2010**, *2*, 192–196; h) N. T. McDougal, S. C. Virgil, B. M. Stoltz, *Synlett* **2010**, 1712–1716.
- [12] This method has been central to the synthesis of a number of natural products in our laboratory: a) (+)-dichroanone: see Ref. [10]; b) (+)-elatol: D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 810–811; c) (–)-cyanthiwigin F: J. A. Enquist, Jr., B. M. Stoltz, *Nature* **2008**, *453*, 1228–1231; d) (+)-carissone: S. R. Levine, M. R. Krout, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 289–292; e) (+)-cassiol: K. V. Petrova, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 293–295; f) (–)-laurencenone C and (–)- α -chamigrene: D. E. White, I. C. Stewart, B. A. Seashore-Ludlow, R. H. Grubbs, B. M. Stoltz, *Tetrahedron* **2010**, *66*, 4668–4686; g) (+)-hamigeran B: H. Mukherjee, N. T. McDougal, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2011**, *13*, 825–827.
- [13] For related approaches from other research groups, see a) M. Braun, F. Laicher, T. Meier, *Angew. Chem.* **2000**, *112*, 3637–3640; *Angew. Chem. Int. Ed.* **2000**, *39*, 3494–3497; b) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847; c) M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem.* **2005**, *117*, 7414–7417; *Angew. Chem. Int. Ed.* **2005**, *44*, 7248–7251; d) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181; e) E. C. Burger, B. R. Barron, J. A. Tunge, *Synlett* **2006**, 2824–2826; f) B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem.* **2006**, *118*, 3181–3184; *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112; g) B. M. Trost, J. Xu, M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282–283; h) É. Bélanger, K. Cantin, O. Messe, M. Tremblay, J.-F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035; i) S. R. Schulz, S. Blechert, *Angew. Chem.* **2007**, *119*, 4040–4044; *Angew. Chem. Int. Ed.* **2007**, *46*, 3966–3970; j) É. Bélanger, C. Houzé, N. Guimond, K. Cantin, J.-F. Paquin, *Chem. Commun.* **2008**, 3251–3253; k) É. Bélanger, M.-F. Pouliot, J.-F. Paquin, *Org. Lett.* **2009**, *11*, 2201–2204; l) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357; m) X. Zhao, D. Liu, F. Xie, W. Zhang, *Tetrahedron* **2009**, *65*, 512–517; n) M. Braun, T. Meier, F. Laicher, P. Meletis, M. Fidan, *Adv. Synth. Catal.* **2008**, *350*, 303–314; o) W.-H. Zheng, B.-H. Zheng, Y. Zhang, X.-L. Hou, *J. Am. Chem. Soc.* **2007**, *129*, 7718–7719; p) X.-X. Yan, C.-G. Liang, Y. Zhang, W. Hong, B.-X. Cao, L.-X. Dai, X.-L. Hou, *Angew. Chem.* **2005**, *117*, 6702–6704; *Angew. Chem. Int. Ed.* **2005**, *44*, 6544–6546.
- [14] For recent reviews on the allylic alkylation of ketone enolates, see a) M. Braun, T. Meier, *Angew. Chem.* **2006**, *118*, 7106–7109; *Angew. Chem. Int. Ed.* **2006**, *45*, 6952–6955; b) S.-L. You, L.-X. Dai, *Angew. Chem.* **2006**, *118*, 5372–5374; *Angew. Chem. Int. Ed.* **2006**, *45*, 5246–5248; c) M. Braun, T. Meier, *Synlett* **2006**, 661–676; d) U. Kazmaier, *Curr. Org. Chem.* **2003**, *7*, 317–328; e) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; f) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476–1491.
- [15] The synthesis of (*R*)-*t*BuPHOX was greatly facilitated by the ready availability of (*R*)-*t*-leucine by the catalytic enantioselective Strecker synthesis reported by Jacobsen and co-workers, see S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968–970.
- [16] H. Miyaoka, H. Nagaoka, T. Okamura, Y. Yamada, *Chem. Pharm. Bull.* **1989**, *37*, 2882–2883.
- [17] Photocycloaddition of enone **5** with acetylene produced a mixture of cyclobutene **8b** and bicyclobutane (–)-**i**, a secondary photoadduct presumably resulting from oxa-di- π -methane rearrangement of **8b** (for an excellent review, see S. S. Hixson, P. S. Mariano, H. E. Zimmerman, *Chem. Rev.* **1973**, *73*, 531–551). Exposure of the mixture to $\text{BF}_3 \cdot \text{OEt}_2$ resulted in conversion of **i** into **8b**. A related bicyclobutane rearrangement to a cyclobutene mediated by AlBr_3 has been reported: V. V. Razin, M. I. Mostova, I. A. D'yakonov, *Zh. Org. Khim.* **1968**, *4*, 535. Although a more complex mixture is believed to result in the case of the photochemical reaction of trimethylsilylacetylene, the three-step process in Scheme 3 is higher yielding (45% versus 68% yield).



- [23] R. L. Cargill, T. E. Jackson, N. P. Peet, D. M. Pond, *Acc. Chem. Res.* **1974**, 7, 106–113.
 - [24] For the thermal rearrangement of a cyclobutene stabilized through vinylogy with an electron-withdrawing substituent, see S. Wakabayashi, Y. Sugihara, Y. Hayakawa, I. Murata, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1489–1490.
 - [25] Hydrogenation of dienes **9** and **3** or alkenes **16–19** did not result in saturation of the trisubstituted olefin or afforded the undesired *cis* ring fusion.
 - [26] Aryl ketone **17** was recovered in 18% yield without epimerization.
 - [27] Initial attempts used CuI, TMEDA/H₂O: M. Carril, R. SanMartin, I. Tellitu, E. Domínguez, *Org. Lett.* **2006**, 8, 1467–1470.
 - [28] For the intramolecular trapping of aryne with a pendant alcohol, see M. A. Birkett, D. W. Knight, P. B. Little, M. B. Mitchell, *Tetrahedron* **2000**, 56, 1013–1023, and references therein.
 - [29] Based on the ¹H NMR spectrum of the crude reaction mixture.
 - [30] G. A. Olah, G. Salem, J. S. Staral, T.-L. Ho, *J. Org. Chem.* **1978**, 43, 173–175.
-