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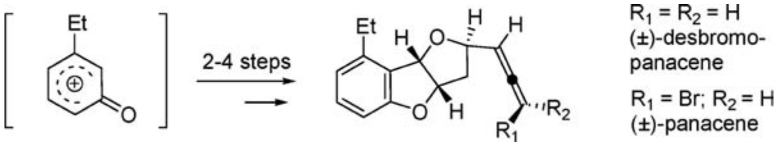

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Expeditious Total Syntheses of Natural Allenic Products via Aromatic Ring Umpolung

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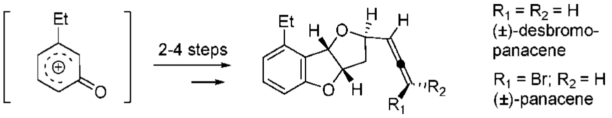
ABSTRACT



Concise diastereoselective syntheses of the marine (±)-panacene and terrestrial (±)-desbromopanacene have been achieved in a few steps based on a concept of "aromatic ring umpolung". The synthetic avenue to the (±)-panacene involved a novel oxymercuration strategy to produce the correct configuration of the bromoallene moiety.

Electron-rich aromatic compounds, such as phenols, anilines, and their derivatives, normally express nucleophilic reactivity. However, oxidative activation[1,2] can convert these aromatics into reactive electrophilic intermediates, which may be intercepted with appropriate nucleophiles in synthetically useful yields. This is exemplified in Figure 1. Thus, oxidative attack of a phenol[3] or an *N*-arylsulfonamide[4] with iodobenzene diacetate (DIB), an environmentally benign and inexpensive reagent, in the presence of, e.g., furan, promotes an oxidative annulation process[5] that furnishes products **4** (Z = O) in 38−69% yield. The erstwhile electron-rich aromatic substrate has expressed electrophilic character in this reaction. The overall transformation may thus be thought of as involving "aromatic ring umpolung" (Figure 1).[6]

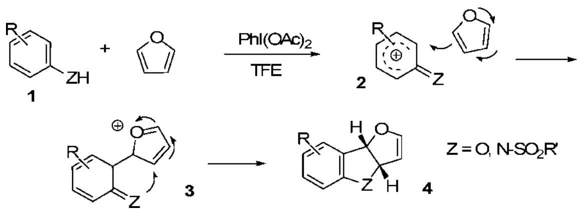


Figure 1. Aromatic ring umpolung.

The concept of aromatic ring umpolung provides new strategic opportunities in synthetic chemistry. In this paper, we illustrate an initial application of the new technique in connection with a fully stereocontrolled total synthesis of

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(1) A key aspect of the potential of DIB is well defined in the work of Kita et al.: (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5854. (d) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481. (e) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698. (f) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469. (g) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787 (outstanding asymmetric version)

(2) (a) Pelter, A.; Drake, R. A. *Tetrahedron Lett.* **1988**, *29*, 4181. (b) Quideau, S.; Looney, M. A.; Pouységu, L. *J. Org. Chem.* **1998**, *63*, 9597. (c) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (d) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065. (e) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318. (f) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem.* **2007**, *119*, 4016. (g) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759. (h) Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076. (i) Bérard, D.; Giroux, M. A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, 7537. (j) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A. M.; Miqueu, K.; Sotiropoulos, J. M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552 (outstanding asymmetric version). (k) Special issue: *Tetrahedron (Symposium-in-Print)* **2001**, *57*, 2.

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(±)-desbromopanacene, **5**, (±)-panacene, **6**,[7] and its unnatural isomer, (±)-epipanacene, **7** (Figure 2). Compound **5** is a plant metabolite isolated in 1915 from *Panax ginseng* and *Panax quinquefolius*.[8] No synthesis of this substance has been reported as of this writing. A marine variant of **5** was isolated in 1977 by Meinwald and co-workers from *Aplysia brasiliana*,[9] a sea hare indigenous to the gulf coast of Florida, and christened as panacene. For this reason, we refer to **5** as desbromopanacene. Panacene has shark antifeedant properties, and it is thus believed to protect the sea hare from predatory fish.

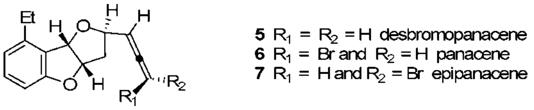
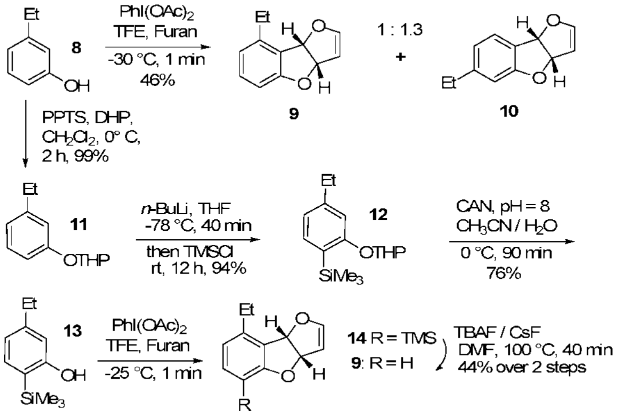


Figure 2. Natural allenic products.

The unusual architecture of **6** has elicited substantial interest in the synthetic arena.[10,11] This has led to total syntheses of the racemate,[10a,b] and of the natural (−)-form[10c] in 17 and 9 steps (from ethyl 6-ethylsalicylate; in 0.7% and 1.5% overall yield, respectively) and 15 steps (from 2-methoxy-6-methylbenzoic acid; 8.3% overall yield), respectively. Our approach, which is based on aromatic ring umpolung, starts with inexpensive 3-ethylphenol **8**. This material may be directly converted into a mixture (1:1.3)[12] of **9** and **10** in 46% yield by DIB oxidation in presence of furan (Scheme 1). A more selective route evolves from derivative **13**, which is readily accessed from **8** in three steps.[13] The TMS group blocks position 6 of the phenol and forces the subsequent oxidative annulation sequence to occur exclusively at position 2. Thus, the core of panacene is assembled in a single step. It is worthy of note that the silyl substituent survives the DIB oxidation step largely unscathed. Indeed, the desired **14** was accompanied by only a small amount (∼5%) of **9** and **10**, which clearly arise through partial loss of the TMS group during the reaction. Without separation, this crude mixture was treated with TBAF and CsF in DMF to induce desilylation.

Scheme 1. Dihydrofurano[2,3-*b*]benzofuran Core



Compound **9** thus emerged in 44% overall yield. Although this route is longer than direct oxidation, it produced **9** with a global yield of 31.1% instead of 20.2% (Scheme 1). Compound **9** was subsequently converted into **15** by an oxymercuration−demercuration sequence. The advantage of the present approach is apparent when considering that intermediate **15**, a known precursor to panacene, was previously synthesized in nine steps from 2-methoxy-6-methylbenzoic acid.[10c] The unsubstituted allene present in "terrestrial" panacene analog **5** was efficiently introduced through a Sakurai reaction[14] of **15** with propargyltrimethylsilane. Compound **5** emerged in 63% yield (Scheme 2). The first total synthesis of this compound was thus achieved in three steps and in 13% global yield from **8**, or in seven steps and 20% yield from **8** via **13**.

The elaboration of **15** to panacene required a method for the stereoselective construction of bromoallene moiety. We focused on a ring opening/ring closing strategy[15] for that

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(4) *N*-Arylsulfonamide activation: (a) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75. (b) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553.

(5) Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238.

(6) The concept of "umpolung" chemistry has been discovered by E. J. Corey and D. Seebach: (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (b) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.

(7) Bromoallene moieties are present in marine natural products: Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.

(8) (a) Kondo, H.; Tanaka, G. *Yakugaku Zasshi (Japan)* **1915**, *401*, 779. (b) Min, P. *Folia Pharmacol. Jpn.* **1931**, *11*, 256. (c) Dembitsy, V. M.; Takashi, M. *Prog. Lipid Res.* **2007**, *46*, 328.

(9) Kinnel, R.; Duggan, A. J.; Eisner, T.; Meinwald, J.; Miura, I. *Tetrahedron Lett.* **1977**, *18*, 3913.

(10) (a) Feldman, K. S.; Mechem, C. C.; Nader, L. *J. Am. Chem. Soc.* **1982**, *104*, 4011. (b) Feldman, K. S. *Tetrahedron Lett.* **1982**, *23*, 3031. (c) Boukouvalas, J.; Pouliot, M.; Robichaud, J.; MacNeil, S.; Snieckus, V. *Org. Lett.* **2006**, *8*, 3597.

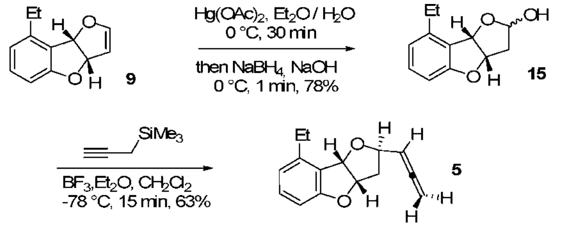
(11) Stuart, J. G.; Nicholas, K. M. *Heterocycles* **1991**, *32*, 949.

(12) Estimated within the resolution limit of ^{1}H NMR analysis (Varian 600 MHz).

(13) Details of the preparation of **13** are provided as Supporting Information. We note that release of the THP ether from **12** was best effected with CAN in acetonitrile as described by: (a) DattaGupta, A.; Singh, R.; Singh, V. K. *Synlett* **1996**, 69. (b) Marko, I. E.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, L.; Wiaux, M. *Tetrahedron Lett.* **1999**, *40*, 5613. Other acidic methods lead to a partial loss of the TMS group.

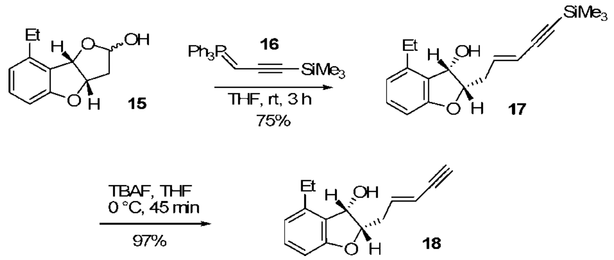
(14) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208.

Scheme 2. Total Synthesis of (±)-Desbromopanacene



purpose. Accordingly, reaction of **15** with Wittig reagent **16**[16] proceeded with good selectivity (9:1) in favor of (*E*)-isomer **17**,[17] which was then desilylated (TBAF) to afford **18** in high yield (Scheme 3).

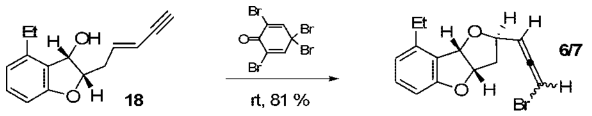
Scheme 3. Ring-Opening/Ring-Closing Strategy



The action of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCD)[18] on compound **18** resulted in formation of a mixture of panacene **6** and epipanacene **7** in high yield.[19] The product ratio[12] proved to be solvent dependent (Table 1): a high degree of diastereoselectivity in favor of epipanacene **7** was attained in apolar solvents such as cyclohexane or benzene. Epipanacene is produced in this manner in only five steps via a direct oxidation of 3-ethyl phenol **8** with a global yield of 8.9% or in nine steps with an overall yield of 14.3%. We note that TBCD appears to be a more selective reagent than *N*-bromosuccinimide, which promoted aromatic ring bromination as a side reaction. Although this method led to an unnatural epimer of panacene, it also signaled that the inherent facial bias present in **18** enables the execution of highly diastereoselective cyclization.

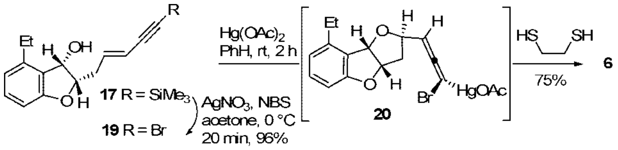
We thus reasoned that the correct relative configuration of the bromoallene moiety could be secured by orchestrating the cyclization of a bromoacetylene derivative of **18** with an appropriate electrophilic reagent. To that end, treatment of **17** with silver nitrate and NBS produced **19**[20] in essentially quantitative yield. Exposure of the latter to Hg(OAc)$_2$ in benzene induced diastereoselective formation of **20**, which was demercurated in situ, with retention of allene configuration, upon contact with ethanedithiol. Totally synthetic (±)-panacene **6** was thus obtained in good yield (Scheme 4).

Table 1. Solvent Influence and Synthesis of (±)-Epipanacene



solvent	time (h)	**6**	**7**
acetonitrile	0.5	0.5	0.5
ethyl acetate	1	0.4	0.6
tert-butyl alcohol	1	0.3	0.7
chloroform	1	0.1	0.9
cyclohexane	5	trace	>0.95
benzene	1.5	trace	>0.95

Scheme 4. Synthesis of (±)-Panacene



We emphasize that thiols are known to promote protiodemercuration of α-mercurio carbonyl compounds under mild conditions.[21] However, their application to the stereoselective demercuration of allenylmercury organometallics with retention of configuration is unprecedented to the best of our knowledge. This could have significant ramifications in the total synthesis of allenic natural products. (±)-Panacene has been reached, by this strategy, for the first time, by a substrate-controlled diastereoselection without using any external asymmetric reagent.

In summary, concise and fully diastereoselective syntheses of "marine" and "terrestrial" (±)-panacenes were accomplished via a formal oxidative [2 + 3] cycloaddition between a substituted phenol and furan. One may thus reach panacene and desbromopanacene in an unprecedented five steps and three steps, respectively, from inexpensive 3-ethylphenol. A more highly regioselective variant of the same approach proceeds in nine and seven steps, respectively, via **13**. Finally, a novel oxymercuration–

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(15) (a) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175. (b) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473.

(16) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, *14*, 1495.

(17) The small amount of (*Z*)-isomer was readily removed by flash chromatography.

(18) Tsubota, M.; Iso, M.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1252.

(19) For an article on the stereochemical course of bromoetherification of enynes, see: Braddock, D. C.; Bhuva, R.; Perez-Fuertes, Y.; Pouwer, R.; Roberts, C. A.; Ruggiero, A.; Stokes, E. S. E.; White, A. J. P. *Chem. Commun.* **2008**, 1419.

(20) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.

(21) (a) Gouzoules, F. H.; Whitney, R. A. *Tetrahedron Lett.* **1985**, *26*, 3441. (b) Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024.

demercuration process has been devised for the construction of the bromoallene segment of panacene. These syntheses demonstrate the potential of “aromatic ring umpolung”, further applications of which are under study in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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