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Alkaloids

Total Synthesis of 7- and 8-Oxygenated Pyrano[3,2-*a*]carbazole and Pyrano[2,3-*a*]carbazole Alkaloids via Boronic Acid-Catalyzed Annulation of the Pyran Ring**

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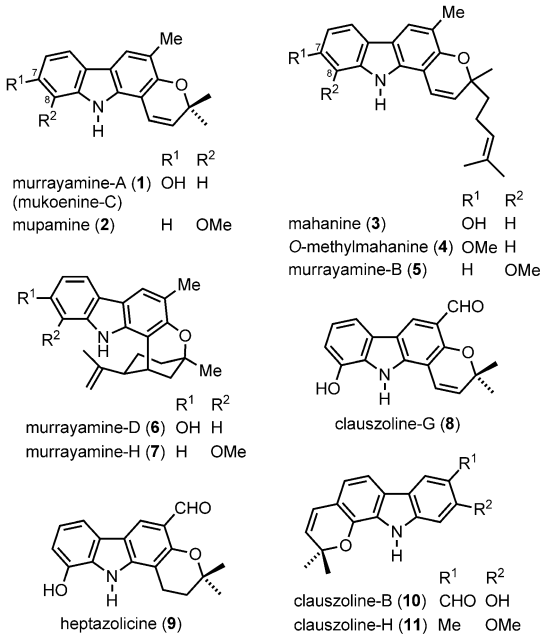
Abstract: The boronic acid-catalyzed annulation of citral opens up a short route to oxygenated cyclized monoterpenoid pyranocarbazole alkaloids. Thus, murrayamine-D is available in only three steps and 55% overall yield from the corresponding carbazole precursor.

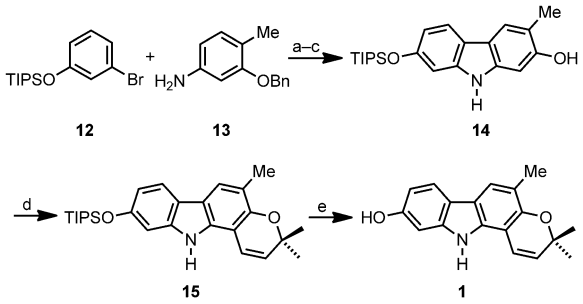
Carbazole alkaloids have been in the focus of research because of their useful biological activities and their structural variety. A broad range of pyrano[3,2-*a*]carbazoles and pyrano[2,3-*a*]carbazoles which are oxygenated at position 7 or 8 has been isolated by Furukawa, Wu and others from plants of the genera *Murraya* and *Clausena* belonging to the family Rutaceae (e.g., compounds **1**–**11**, Scheme 1).[1] Many synthetic approaches to pyranocarbazoles have been developed but only a few routes to the more highly oxygenated derivatives have been reported.[1–3] Herein, we describe an efficient access to the 7- and 8-oxygenated pyrano[3,2-*a*]carbazole and pyrano[2,3-*a*]carbazole alkaloids **1**–**11** featuring our palladium-catalyzed construction of the carbazole nucleus and a boronic acid-catalyzed annulation of the pyran ring as key steps.

The two-step palladium-catalyzed approach, synthesis of a diarylamine and oxidative cyclization, provides a broad access to carbazole alkaloids including 2,7- and 2,8-dioxygenated derivatives.[4,5] Thus for the synthesis of the 7-oxygenated pyrano[3,2-*a*]carbazole alkaloids, Buchwald–Hartwig coupling[6] of the bromoarene **12** and the arylamine **13** followed by palladium(II)-catalyzed oxidative cyclization and removal of the benzyl protecting group afforded the 2-hydroxycarbazole **14** (Scheme 2).

Various methods for annulation of a *gem*-dimethylpyran ring have been developed.[7] Recently, we have applied the Lewis acid-promoted annulation of prenal (Casiraghi's method)[8] for the synthesis of pyranocarbazoles.[9] However, this procedure uses an excess of titanium tetraisopropoxide, reaction conditions which appeared to be too harsh for the present target compounds (**1**–**11**). A promising procedure for annulation of *gem*-dimethylpyran rings is the phenylboronic acid-mediated



Scheme 1. Structures of the naturally occurring 7- and 8-oxygenated pyrano[3,2-*a*]carbazole and pyrano[2,3-*a*]carbazole alkaloids **1**–**11**.



Scheme 2. Synthesis of murrayamine-A (mukoenine-C) (**1**): a) 6 mol% $Pd(OAc)_2$, 6 mol% *rac*-BINAP, 1.4 equiv Cs_2CO_3, toluene, reflux, 20 h (99%); b) 10 mol% $Pd(OAc)_2$, 2.5 equiv $Cu(OAc)_2$, HOAc, MW (300 W), 130 °C, 2 h (77%); c) 10% Pd/C, H_2 (1 atm), MeOH/CH_2Cl_2 (2.5:1), RT, 24 h (100%); d) 1.5 equiv prenal, 20 mol% $PhB(OH)_2$, 110 equiv EtCOOH, toluene, reflux, 36 h (63%); e) 1.6 equiv TBAF, DMF, 0 °C, 5 min (95%).

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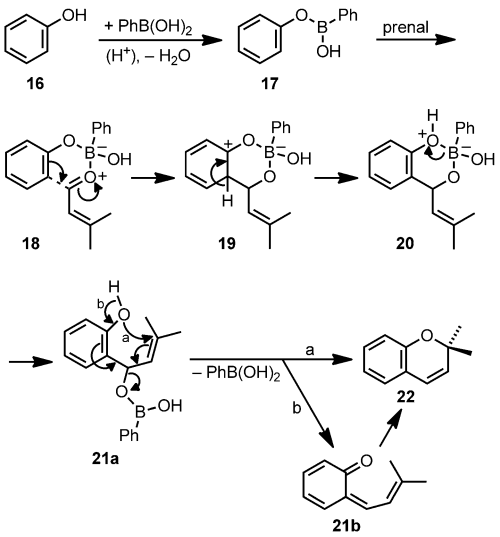
reaction of phenols with prenal which has been applied to the synthesis of chromenes.[10] Reaction of the 2-hydroxycarbazole **14** with prenal using the conditions described by Snieckus et al. (stoichiometric amounts of phenylboronic acid in the presence of an excess of acetic acid)[10b] afforded *O*-triisopropylsilylmurrayamine-A (**15**) in only 37% yield (Table 1). Using stoichiometric amounts of phenylboronic acid in the presence of an excess of propanoic acid, conditions reported to give better results,[10a,d] provided compound **15** in up to 69% yield. Finally, reaction of **14** with prenal in the presence of only 20 mol% of phenylboronic acid and an excess of propanoic acid led to **15** in 63% yield. Removal of the silyl group afforded murrayamine-A (**1**), isolated in 1991 by Wu from the leaves of *Murraya euchrestifolia*.[11] Only two years later, Furukawa and co-workers isolated compound **1** from the roots of *Murraya koenigii* and named it mukoenine-C.[12]

Table 1. Boronic acid-catalyzed annulation of prenal to *O*-(triisopropylsilyl)murrayamine-A (**15**).

$PhB(OH)_2$ [equiv]	Reaction conditions[a]	**15**, Yield [%]
1.5	88 equiv MeCOOH, 24 h	37
1.5	110 equiv EtCOOH, 24 h	50
1.5	110 equiv EtCOOH, 36 h	69
0.2	110 equiv EtCOOH, 36 h	63

[a] 1.5 equiv prenal, toluene, reflux.

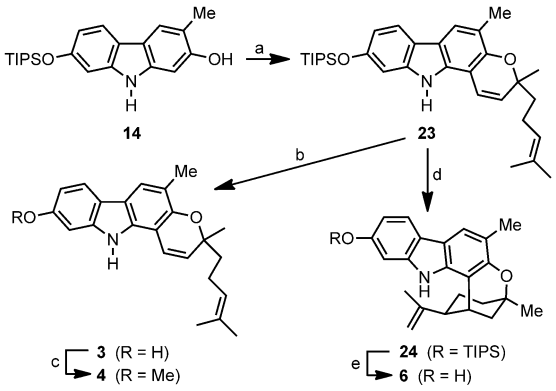
We suggest the following mechanism for the boronic acid-catalyzed pyran annulation (Scheme 3). Phenol **16** is transformed to a boronic ester **17** and then by reaction with prenal via the intermediates **18**, **19**, and **20** to the *ortho*-prenylated phenol **21a**. Cyclization of **21a** via an S_N2'-type reaction would lead directly to the 2*H*-chromene **22** (path a). Alternatively, 1,4-elimination may lead to the dienone **21b** which affords **22** on electrocyclic ring closure (path b).[10d] In any case, phenylboronic acid is regenerated for the catalytic cycle.



Scheme 3. Proposed mechanism for the boronic acid-catalyzed annulation of the 2,2-dimethylpyran ring.

Reaction of the 2-hydroxycarbazole **14** with citral in the presence of 20 mol% of boronic acid and an excess of propanoic acid afforded the desired *O*-(triisopropylsilyl)mahanine (**23**) in 51% yield along with *O*-(triisopropylsilyl)murrayamine-D (**24**) in 27% yield (Scheme 4, Table 2). The proton-catalyzed conversion of homoprenyl-substituted pyrano[3,2-*a*]carbazoles to the corresponding cyclized monoterpenoid pyrano[3,2-*a*]carbazoles has been confirmed recently.[9] Therefore, we aimed at a boronic acid-catalyzed pyran annulation without additional Brønsted acid as additive. Treatment of **14** with citral in the presence of 20 mol% phenylboronic acid in toluene at reflux for three days provided compound **23** in 75% yield. Removal of the silyl group led to mahanine (**3**), which has been isolated repeatedly from different plants of the Rutaceae family.[11,13] Mahanine (**3**) exhibits a range of useful biological activities (e.g., antimutagenic, antioxidant, antitumor).[13,14] O-Methylation of **3** provided *O*-methylmahanine (**4**), obtained in 2003 by Nakatani et al. from the leaves of *Murraya koenigii*.[15,16] On the other hand, treatment of **23** with Brønsted acid using our previously optimized reaction conditions[9] induced a smooth conversion into **24**. Fluoride-promoted desilylation of **24** provided murrayamine-D (**6**), isolated in 1995 by Wu et al. from the leaves of *Murraya euchrestifolia* collected during winter.[17]

For the synthesis of 8-oxygenated pyrano[3,2-*a*]carbazole alkaloids, we used the bromoarene **25** as precursor (Scheme 5). The sequence of Buchwald–Hartwig coupling with **13**, palladium(II)-catalyzed oxidative cyclization and benzyl group removal afforded carbazole **26**. Annulation of the pyran ring by boronic



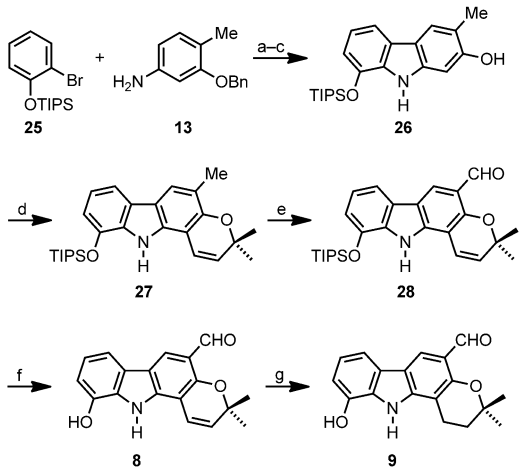
Scheme 4. Synthesis of mahanine (**3**), *O*-methylmahanine (**4**), and murrayamine-D (**6**): a) 1.5 equiv citral, 20 mol% $PhB(OH)_2$, toluene, reflux, 3 d (75%); b) 1.6 equiv TBAF, DMF, 0 °C, 30 min (98%); c) 1.3 equiv NaH, 1.0 equiv MeI, THF, RT, 24 h (60%); d) 0.5 equiv TFA, toluene, RT, 16.5 h (80%); e) 1.4 equiv TBAF, DMF, 0 °C, 30 min (92%).

Table 2. Boronic acid-catalyzed annulation of citral to *O*-(triisopropylsilyl)-mahanine (**23**).

Reaction conditions[a]	Yield [%]
20 mol% $PhB(OH)_2$, 110 equiv EtCOOH, 18 h	51, **23**; 27, **24**
20 mol% $PhB(OH)_2$, 3 d	75, **23**

[a] 1.5 equiv citral, toluene, reflux.

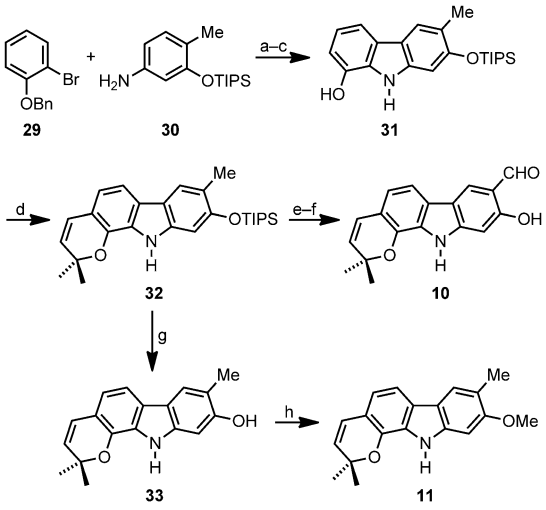
acid-catalyzed reaction with prenal provided the 8-oxygenated pyrano[3,2-*a*]carbazole **27**. Oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded **28** which on removal of the silyl group gave clauszoline-G (**8**), isolated by Ito et al. from the stem bark of *Clausena excavata*.[18] Catalytic hydrogenation of **8** led to heptazolicine (**9**), isolated by Chowdhury et al. from the roots of *Clausena heptaphylla*.[19,20]



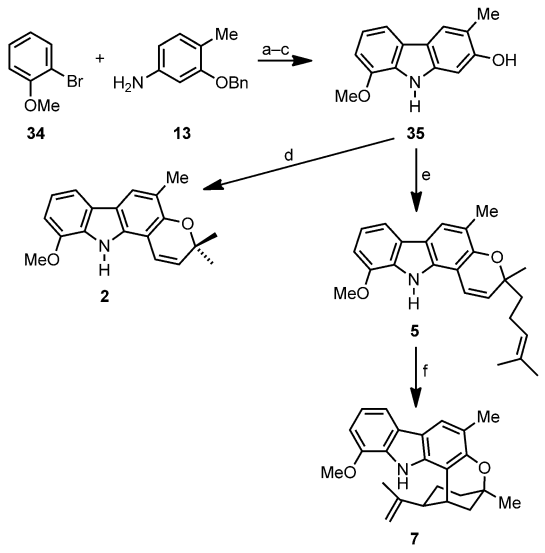
Scheme 5. Synthesis of clauszoline-G (**8**) and heptazolicine (**9**): a) 6 mol% $Pd_2(dba)_3$, 12 mol% DavePhos, 1.2 equiv NaO*t*Bu, toluene, reflux, 24 h (98%); b) 20 mol% $Pd(OAc)_2$, 20 mol% K_2CO_3, HOPiv, air, 85 °C, 20 h (85%); c) 10% Pd/C, H_2 (1 atm), MeOH/CH_2Cl_2 (4:1), RT, 3 d (100%); d) 1.5 equiv prenal, 20 mol% $PhB(OH)_2$, 110 equiv EtCOOH, toluene, reflux, 21 h (76%); e) 2.2 equiv DDQ, MeOH/THF/H_2O (4:1.5:1), 45 °C, 3 h (64%); f) 1.6 equiv TBAF, DMF, 0 °C, 5 min (93%); g) 10% Pd/C, H_2 (1 atm), MeOH/CH_2Cl_2 (3:1), RT, 3 d (68%).

The synthesis of the pyrano[2,3-*a*]carbazole alkaloids **10** and **11** required a protecting group reversal, as removal of the benzyl group by hydrogenolysis should be done prior to annulation of the pyran ring. Coupling of the bromoarene **29** and the arylamine **30** by the sequence of Buchwald–Hartwig reaction and palladium(II)-catalyzed cyclization was followed by hydrogenolysis to afford the 8-hydroxycarbazole **31** (Scheme 6). Boronic acid-catalyzed reaction of **31** with prenal led to the pyrano[2,3-*a*]carbazole **32**. Oxidation of **32** with DDQ and subsequent removal of the silyl group provided clauszoline-B (**10**), isolated by Ito et al. from the stem bark of *Clausena excavata*.[18] Fluoride-promoted desilylation of **32** to compound **33** followed by O-methylation provided clauszoline-H (**11**), obtained by Ito et al. from the roots of *Clausena excavata*.[21]

Next, we have developed a total synthesis of the 8-methoxy-substituted pyrano[3,2-*a*]carbazole alkaloids **2**, **5**, and **7** (Scheme 7). Buchwald–Hartwig coupling of *o*-bromoanisole (**34**) and arylamine **13** followed by palladium(II)-catalyzed cyclization and benzyl hydrogenolysis afforded carbalexin-B (**35**). Greger et al. described the stress-induced formation of this phytoalexin in *Glycosmis parviflora* and isolated it from the leaves of that plant.[22,23] Carbalexin-B (**35**) exhibits a strong antifungal activity. Boronic acid-catalyzed reaction of **35** with prenal led to mupamine (**2**), isolated by Mester and Reisch from the root bark of *Clausena anisata*.[23,24] The structural assignment for our synthetic mupamine (**2**) has been additionally confirmed by an X-ray crystal structure determination (Figure 1).[25] The boronic acid-catalyzed annulation of **35** and citral provided murrayamine-B (**5**), isolated by Wu from the leaves of *Murraya euchrestifolia*.[11] Finally, cyclization of **5** in the presence of trifluoroacetic acid led to murrayamine-H (**7**). Mur-



Scheme 6. Synthesis of clauszoline-B (**10**) and clauszoline-H (**11**): a) 10 mol% $Pd(OAc)_2$, 10 mol% *rac*-BINAP, 1.4 equiv Cs_2CO_3, toluene, reflux, 21 h (82%); b) 20 mol% $Pd(OAc)_2$, 20 mol% K_2CO_3, HOPiv, air, 85 °C, 26 h (70%); c) 10% Pd/C, H_2 (1 atm), MeOH/CH_2Cl_2 (4:1), RT, 3 d (95%); d) 1.5 equiv prenal, 20 mol% $PhB(OH)_2$, 110 equiv EtCOOH, toluene, reflux, 3 d (78%); e) 1.5 equiv DDQ, MeOH/THF/H_2O (4:1:1), RT, 30 min (32%); f) 1.6 equiv TBAF, DMF, 0 °C, 10 min (75%); g) 1.6 equiv TBAF, DMF, 0 °C, 10 min; h) 1.3 equiv NaH, 1.0 equiv MeI, THF, 0 °C to RT, 24 h (80% over 2 steps).



Scheme 7. Synthesis of mupamine (**2**), murrayamine-B (**5**), and murrayamine-H (**7**): a) 10 mol% $Pd(OAc)_2$, 20 mol% XPhos, 1.4 equiv Cs_2CO_3, toluene, reflux, 24 h (98%); b) 10 mol% $Pd(OAc)_2$, 10 mol% K_2CO_3, HOPiv, air, 85 °C, 24 h (60%); c) 10% Pd/C, H_2 (1 atm), MeOH/CH_2Cl_2 (2:1), RT, 5 d (64%); d) 1.5 equiv prenal, 20 mol% $PhB(OH)_2$, 110 equiv EtCOOH, toluene, reflux, 48 h (82%); e) 1.5 equiv citral, 20 mol% $PhB(OH)_2$, toluene, reflux, 48 h (81%); f) 1.5 equiv TFA, toluene, RT, 24 h (60%).

rayamine-H (**7**) was isolated by Wu et al. from the leaves of *Murraya euchrestifolia* collected in May,[26] whereas murrayamine-D (**6**) was isolated from the leaves of the same plant collected in winter.[17] The seasonal variation of carbazole alkaloids in the leaves of this traditional Chinese medicinal plant has been suggested as an explanation for the observation that the pharmacological activity of the extracts is strictly dependent on the collection time.[26] An optical activity for murrayamine-D (**6**) and -H (**7**) was not reported.

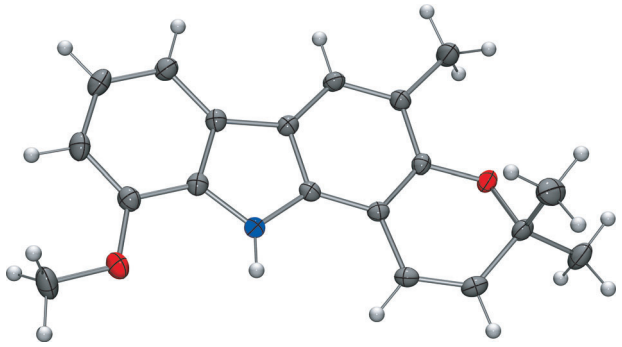


Figure 1. Molecular structure of mupamine (**2**) in the crystal (ORTEP plot showing thermal ellipsoids at the 50% probability level).

In conclusion, we have shown that the boronic acid-catalyzed annulation of the pyran ring provides an efficient access to the 7- and 8-oxygenated pyrano[3,2-*a*]carbazole and pyrano[2,3-*a*]carbazole alkaloids **1**–**11**. For eight of these alkaloids we have described the first total synthesis: murrayamine-A (mukoenine-C) (**1**), mahanine (**3**), murrayamine-B, -D, -H (**5**–**7**), and clauszoline-G, -B, and -H (**8**, **10**, **11**). The spectroscopic data for our synthetic compounds **1**–**11** are in full agreement with those reported for the natural products, thus confirming the previous structural assignments. A more detailed investigation of the promising pharmacological potential of this class of compounds is now feasible.

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Keywords: alkaloids · C–H bond activation · natural products · palladium · stereoselective catalysis

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[25] Crystallographic data for mupamine (**2**): $C_{19}H_{19}NO_2$, $M=293.35\ g\,mol^{-1}$, crystal size: $0.40\times0.32\times0.05\ mm^3$, orthorhombic, space group *Pbca*, $a=10.3979(7)$, $b=13.0118(9)$, $c=22.6721(16)$ Å, $V=3067.4(4)$ Å^3, $Z=8$, $\rho_{calcd}=1.270\ g\,cm^{-3}$, $\mu=0.082\ mm^{-1}$, $\lambda=0.71073$ Å, $T=150(2)$ K, θ range $=1.80-28.37^\circ$, reflections collected: 76681 independent: 3783 ($R_{int}=0.0735$), 207 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices [$I>2\sigma(I)$]: $R_1=0.0375$; $wR_2=0.0937$; maximal residual electron density: $0.257\ e\,Å^{-3}$. CCDC-990676 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

[26] T.-S. Wu, M.-L. Wang, P.-L. Wu, *Phytochemistry* **1996**, *43*, 785.

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COMMUNICATION

Alkaloids

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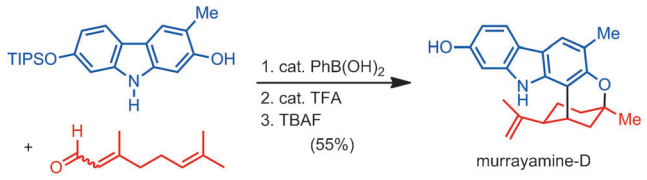
Total Synthesis of 7- and 8-Oxygenated Pyrano[3,2-*a*]carbazole and Pyrano[2,3-*a*]carbazole Alkaloids via Boronic Acid-Catalyzed Annulation of the Pyran Ring



Efficient process: The boronic acid-catalyzed annulation of citral opens up a short route to oxygenated cyclized monoterpenoid pyranocarbazole alkaloids. Thus, murrayamine-D is available in only three steps and 55% overall yield from the corresponding carbazole precursor.

A space filling model…of the X-ray structure of the pyrano[3,2-*a*]carbazole alkaloid mupamine is shown. Its synthesis, which involves the boronic acid-catalyzed annulation of citral, is described in the Communication by H.-J. Knölker et al. on page ■■ ff.