HETEROCYCLES, Vol. 70, 2006, pp. 309 - 319. © The Japan Institute of Heterocyclic Chemistry
Received, 11th August, 2006, Accepted, 6th November, 2006, Published online, 7th November, 2006. COM-06-S(W)24

SYNTHESIS OF 2,3-DIHYDROBENZO[1,4]DIOXINS AND –OXAZINS *VIA* A DOMINO WACKER-HECK REACTION

Lutz F. Tietze*[a], Kristina F. Wilckens[a], Sinem Yilmaz[a], Florian Stecker[a], and Julia Zinngrebe[a]

[a] Prof. Dr. h. c. L. F. Tietze, Dipl.-Chem. K. W. Wilckens, Stud.-Chem. Sinem Yilmaz, Dipl.-Chem. F. Stecker, Dipl.-Chem. J. Zinngrebe, Institute of Organic and Biomolecular Chemistry, Georg-August-University Göttingen, Tammannstraße 2, D-37077 Göttingen (Germany), E-mail: ltietze@gwdg.de, Fax: +49 (0)551 / 39 94 76

Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

Abstract – An efficient and operationally simple domino Wacker-Heck reaction of allylic phenols and α,β-unsaturated ketones as well as esters in the presence of catalytic amounts of $Pd(TFA)_2$ and an oxidant for the synthesis of 2,3-dihydrobenzo[1,4]dioxins and 2,3-dihydrobenzo[1,4]oxazins is described. The necessary substrates are prepared by monoallylation of catechol derivatives and *ortho*-aminophenol.

INTRODUCTION

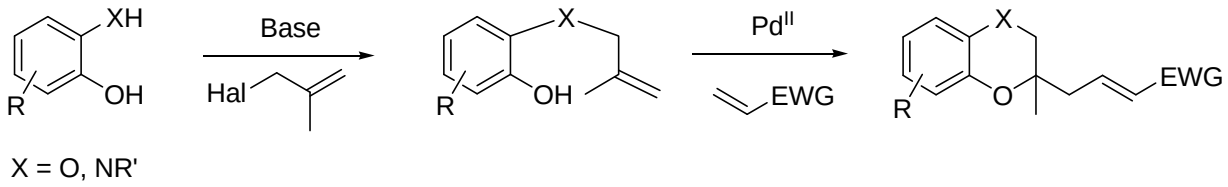
In the last decades the most important aim in organic synthesis was the chemo-, regio-, diastereo- and enantioselective preparation of organic compounds. However, in recent years there had been a change of paradigm; synthetic efficiency is nowadays a central issue. So far, the usual synthetic procedure was based on the stepwise formation of individual bonds with workup steps after each transformation. Today modern synthesis management must seek for procedures that allow the formation of several bonds, either C-C, C-O or C-N bonds in one process. In an ideal procedure, the entire transformation should be run without the addition of any further reagent or catalyst and without changing the reaction conditions. We have defined this type of transformations as “domino reaction” or “domino process”.[1]

According to these lines, we recently developed an enantioselective transition metal-catalyzed domino reaction for the synthesis of vitamin E.[2] This transformation is based on an intramolecular Pd^{II}-catalyzed

addition of a phenolic hydroxyl group to a C=C-double bond in the presence of a chiral BOXAX ligand [3], followed by an intermolecular addition of the intermediate Pd-species to the double bond of an α,β-unsaturated ketone or carboxylate present in the reaction mixture. Here, we report the application of this novel domino process for the synthesis of 2,3-dihydrobenzo[1,4]dioxins and analogous *N*-heterocycles derived from catechols and *ortho*-aminophenol, respectively.

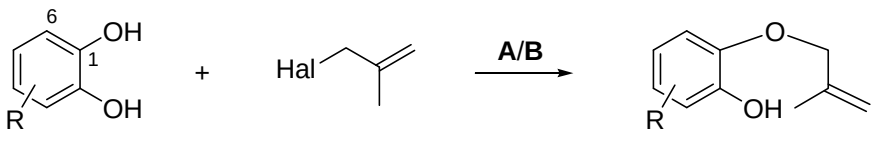
RESULTS AND DISCUSSION

The precursors for the domino reactions were prepared by monoallylation of the corresponding catechols and *ortho*-aminophenol with methallyl halides in presence of a base (Scheme 1).[4,5]



Scheme 1. Synthesis of precursors and subsequent domino reactions for the synthesis of 2,3-dihydrobenzo[1,4]dioxins and 2,3-dihydrobenzo[1,4]oxazins. All chiral compounds were prepared as racemic mixtures.

Reaction of catechols (**1**–**9**) with methallyl halide (**26**) in acetone in the presence of potassium carbonate led to the mono ethers (**10**–**14**) and (**19**–**22**) in 48–67 % yield (Table 1). In contrast, under these conditions the substrates (**6** and **7**) containing a nitro or a cyano group had the tendency to give the bisallylated products preferentially. However, the desired products (**15**/**23**) and (**16**/**24**) could be prepared from **6** and **7** using sodium hydride in DMF in 54 % and 58 % yield, respectively. Moreover, using these conditions also the highly hindered catechols **(8** and **9**) could be monoallylated to give compounds (**17**/**25** and **18**) in 47 and 51 % yield. All catechol mono ethers except **10** were obtained as mixtures of regioisomers. In some cases separation was possible by column chromatography.

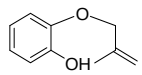
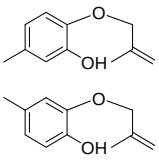
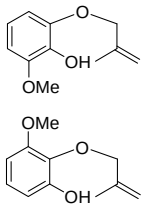
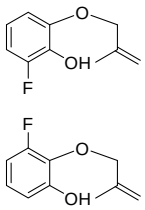
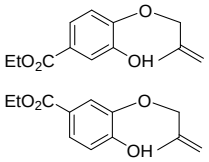
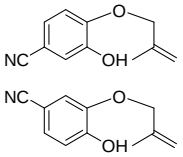
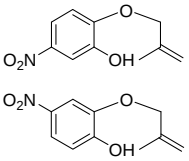
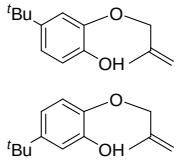
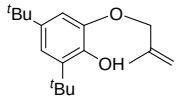


1–**9** **26**: Hal = Cl, Br **10**–**25**

A: 1) 1.0–1.1 eq. K_2CO_3, KI/TBAI, acetone, rt; 2) 1.1–1.2 eq. **26**, reflux.
B: 1) 0.95 eq. NaH, DMF, 0°C → rt; 2) 1.1 eq. **26**, TBAI, 25–80°C.

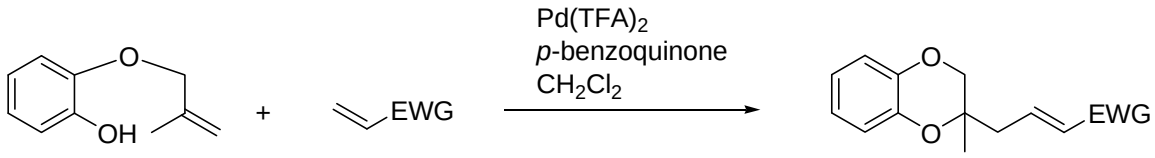
Scheme 2. Synthesis of the monoallyl ethers (**10**–**25**).

Table 1. Monoallylation of catechol derivatives (**1**–**9**) according to Scheme 2.

R	substrate	product		condition	yield [%]
H	**1**		**10**	A	53
4-Me	**2**		**11** **19**	A	63
3-OMe	**3**		**12** **20**	A	67*
3-F	**4**		**13** **21**	A	56*
4-CO_2Et	**5**		**14** **22**	A	48*
4-CN	**6**		**15** **23**	B	54
4-NO_2	**7**		**16** **24**	B	58
4-^{t}Bu	**8**		**17** **25**	B	47
3,5-di^{t}Bu	**9**		**18**	B	51

*partially separable

The reaction conditions for the domino Wacker-Heck reactions of the monoally phenyl ethers to give the corresponding 2,3,-dihydrobenzo[1,4]dioxins were optimized using phenol (**10**) and different α,β-unsaturated acceptors. While ketone (**27**) and the esters (**28** and **29**) led to the expected products (**31**, **32** and **33**) in 72–88 % yield, reaction of **10** with acrylonitrile (**30**) yielded **34** as a mixture of double bond isomers in only 53 % yield. Allylic alcohols or simple alkenes did not afford the desired products.



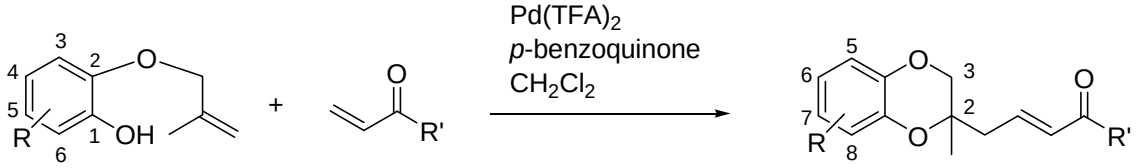
10

27: EWG = $COCH_3$
28: EWG = CO_2Me
29: EWG = CO_2Et
30: EWG = CN

31: 88 %
32: 88 %
33: 72 %
34: 53 % (*E*/*Z* = 5:1)

Scheme 3. Reaction of **10** with differently substituted alkenes as acceptors.

Due to the excellent results obtained for the reaction of **10** with methyl vinyl ketone (**27**) and methyl acrylate (**28**) these compounds were used in the further investigations with the other substituted phenolic substrates, where a strong effect of the substituent on the reactivity was found (Table 2). In the case of the 6-OMe-substituted phenol (**12**), the corresponding product (**35**) was obtained after 5 h at room temperature in 78 % yield, whereas the reaction of the sterically demanding substrate (**18**) required 4 d at 60 °C. Very good results were obtained for substrates bearing an electron-withdrawing group such as **15**/**23** and **16**/**24** (89–93 %), whereas electron-rich systems gave lower yields.



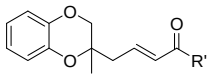
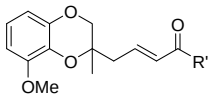
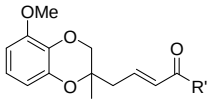
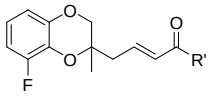
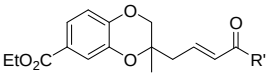
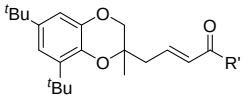
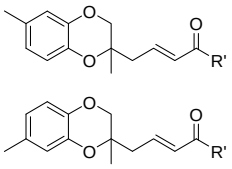
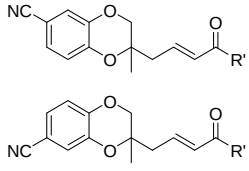
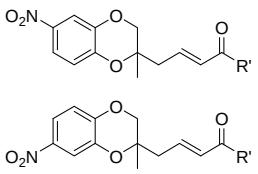
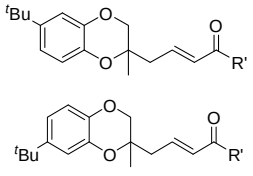
10–**25**, **23**–**25**

27: R' = CH_3
28: R' = OMe

31, **35**–**47**: R' = CH_3
32, **48**–**60**: R' = OMe

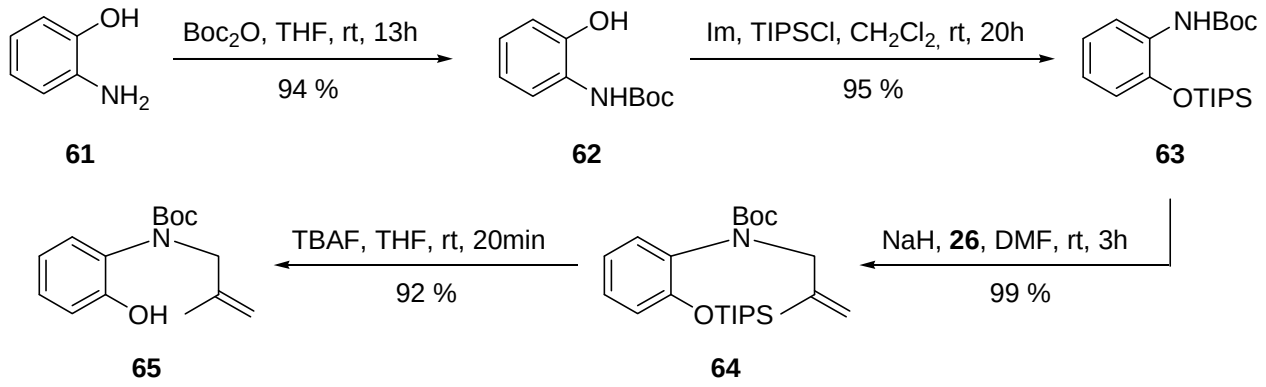
Scheme 4. Synthesis of 2,3-dihydrobenzo[1,4]dioxin-derivatives.

Table 2. Synthesis of 2,3-dihydrobenzo[1,4]dioxins by a domino Wacker-Heck reaction according to Scheme 4.

substrate	product	R' = CH_3[a]	yield [%]	R' = OMe[b]	yield [%]
10		**31**	88	**32**	88
12		**35**	78	**48**	69
20		**36**	74	**49**	48
13		**37**	74	**50**	73
14		**38**	89	**51**	84
18		**39**	68	**52**	86
11/**19**		**40** **41**	80	**53** **54**	80
15/**23**		**42** **43**	91	**55** **56**	93
16/**24**		**44** **45**	93	**57** **58**	89
17/**25**		**46** **47**	85	**59** **60**	84

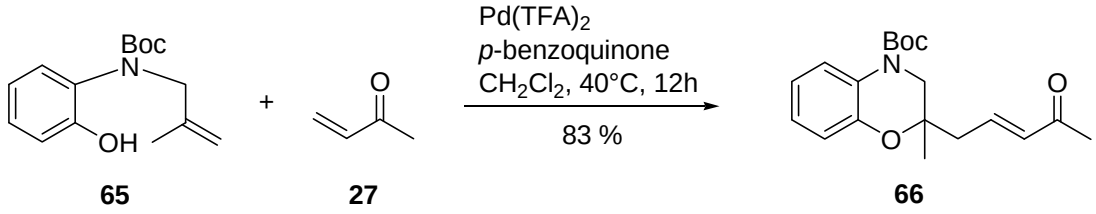
[a]Reaction with methyl vinyl ketone (**27**); [b]Reaction with methyl acrylate (**28**)

For the synthesis of 2,3-dihydrobenzo[1,4]oxazins and to investigate the effect of the heteroatom on the reactivity, phenol (**65**) was prepared starting from *ortho*-aminophenol (**61**). Selective *N*-Boc-protection and subsequent TIPS-protection of the phenolic hydroxyl group in **62** set the stage for the *N*–allylation with **26** to give **64**. Finally, cleavage of the TIPS-ether yielded phenol (**65**) in 81 % over four steps (Scheme 5).[6]



Scheme 5. Synthesis of phenol (**65**)**.**

The domino reaction of *N*-allylic phenol (**65**) proceeded within 12 h at 40 °C to give **66** in 83 % yield (Scheme 6).



Scheme 6. Domino reaction for the synthesis of 2,3-dihydrobenzo[1,4]oxazin (**66**).

CONCLUSION

We have reported on an innovative, efficient and operationally simple synthesis of 2,3-dihydrobenzo[1,4]dioxins and 2,3-dihydrobenzo[1,4]oxazins starting from allylic catechol derivatives and *ortho*-aminophenol. The transformation is based on a domino Wacker-Heck reaction, in which a mixture of the phenols and an α,β-unsaturated ketone or ester are treated with catalytic amounts of $Pd(TFA)_2$ in the presence of an oxidant. Electron-rich phenols turned out to be most reactive, however best yields were obtained with electron-poor systems though at higher temperatures and longer reaction times.

EXPERIMENTAL

General: All reactions were performed under argon in flame-dried flasks. All solvents were dried and distilled prior to use by usual laboratory methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on precoated silica gel SIL G/UV_{254} plates (Macherey–Nagel GmbH & Co. KG) and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Phosphomolybdic acid in methanol (PMA) or vanillin in methanolic sulfuric acid were used as staining reagents for TLC. UV spectra were taken in CH_3CN or MeOH with a Perkin–Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films with a Bruker IFS 25 spectrometer. ^1H and ^{13}C NMR spectra were recorded with Mercury–200, VXR–200, Unity–300, Inova–500, Unity Inova–600 (Varian) or AMX 300 (Bruker) spectrometer. Chemical shifts are reported in ppm with tetramethylsilane (TMS) as internal standard. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured with a Finnigan MAT 95, TSQ 7000 or LCQ instrument.

In the experimental section the general procedures for the synthesis of the substrates and the domino Wacker-Heck reaction are given. In addition, the synthesis of **10** and its transformation to the dioxins (**31** and **32**) as well as the synthesis of **65** and its transformation to the oxazin (**66**) are given in detail. All other syntheses can be obtained from the supporting material.

General Procedure A: **Allylation using K_2CO_3:** A suspension of anhydrous K_2CO_3 (0.95–1.1 eq.) and KI (1.1 eq.), or alternatively TBAI (cat.), in acetone (2 mL/mmol substrate) was treated with the respective substrate and stirred at room temperature until the end of gas release. Afterwards the allyl halide (**26**) (1.1–2.0 eq.) was added and the resulting mixture stirred for 0.5–6 h at 25–60 °C. (TLC-Control). Then H_2O (5 mL/mmol) was added, the solution was neutralised with 1 N HCl and the aqueous phase was extracted with Et_2O (3 × 5 mL/mmol). The combined organic layers were dried over $MgSO_4$, the solvent removed under vacuum and the crude product purified by column chromatography on silica.

General Procedure B: **Allylation using NaH:** The substrate, dissolved in dry DMF (3 mL/mmol), was carefully treated with NaH (0.95 eq.) at 0 °C. After warming up to room temperature and the end of gas release, the respective ally halide (**26**) as well as TBAI (cat.) were added and the reaction mixture stirred for 2–24 h at 25–80 °C (TLC-Control). Then H_2O (5 mL/mmol) was added, the solution neutralised with 1 N HCl and the aqueous phase extracted with Et_2O (3 × 5 mL/mmol). The combined organic layers were washed with H_2O (15 mL/mmol) and saturated NaCl-solution, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica.

General Procedure C: **Domino Wacker-Heck Reaction:** A mixture of palladium trifluoroacetate (0.1

eq.) and *p*-benzoquinone (4.0 eq.) in CH_2Cl_2 (0.4–0.5 mL/mmol substrate) was stirred for 10 min at room temperature. Then a solution of the phenol (1.0 eq.) and the respective coupling partner (2.0–5.0 eq.) in CH_2Cl_2 (0.4–0.5 mL/mmol) was added to the suspension and the mixture was stirred for 5 h–4 d at 25–60 °C. (TLC-Control). At the end of the reaction the mixture was treated with 1N HCl (50 mL/mmol) and the aqueous phase extracted with Et_2O (3 x 50 mL/mmol). The combined organic phases were washed with 1N NaOH (3 x 50 mL/mmol), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica.

2-(2-Methylallyloxy)-phenol (10): According to general procedure **A**, catechol (**1**) (5.01 g, 45.5 mmol) was treated with K_2CO_3 (6.92 g, 50.1 mmol, 1.1 eq.), KI and 3-chloro-2-methylpropene (**26**) (4.94 g, 54.6 mmol, 5.34 mL, 1.2 eq.) under reflux for 4 h. After column chromatography on silica (P/EtOAc = 50:1 → 10:1) the desired compound (**10**) (3.90 g, 23.8 mmol, 52 %) was obtained as a colorless liquid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3 H, 2'-CH_3), 4.51 (s, 2 H, 1'-H_2), 5.03 (m_c, 1 H, 3'-H), 5.10 (m_c, 1 H, 3'-H), 5.70 (s, 1 H, OH), 6.79–6.99 (m, 4 H, Ar-H) ppm. **^{13}C-NMR** (75.6 MHz, $CDCl_3$): δ = 19.37 (2'-CH_3), 72.59 (C-1'), 113.30 (C-3'), 112.11, 114.62 (C-3, C-6), 120.02, 121.63 (C-4, C-5), 140.38 (C-2') 145.60, 145.78 (C-1, C-2) ppm. **IR** (Film): $\tilde{\nu}$ = 3536, 2919, 1597, 1501, 1454, 1373, 1259, 1219 cm^{-1}. **UV** (CH_3CN): λ_{max} (lg ε) = 197.0 (4.582), 199.5 (4.582), 215.5 (3.798), 276.0 (3.424) nm. **MS** (EI, 70 eV): m/z (%) = 164 (57) $[M]^+$, 109 (30) $[M–C_4H_7]^+$, 55 (100) $[C_4H_7]^+$. Calcd for **$C_{10}H_{12}O_2$**: 164.0837, Found: 164.0837 (EI-HRMS).

(2-Hydroxyphenyl)-(2-methylallyl)-carbamic acid *tert*-butyl ester (65): TBAF·3 H_2O (1.91 g, 6.05 mmol, 1.25 eq.) was added to a solution of **64** (2.03 g, 4.84 mmol) in THF (50 mL) and the resulting mixture was stirred for 15 min at room temperature. Afterwards the solvent was removed in vacuum and the crude product filtered over silica (P/EtOAc = 30:1 → 5:1) to yield alkene (**65**) (1.17 g, 4.44 mmol, 92 %) as a colorless crystalline solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, $C(CH_3)_3$), 1.72 (s, 3 H, 2'-CH_3), 4.16 (s, 2 H, 1'-H_2), 4.84–4.90 (m_c, 2 H, 3'-H_2), 6.90 (dt, J = 7.4, 1.5 Hz, 1 H, 5-H), 7.01 (dd, J = 8.2, 1.2 Hz, 1 H, 3-H), 7.10–7.19 (m, 2 H, 4-H, 6-H) ppm. **^{13}C-NMR** (75.6 MHz, $CDCl_3$): δ = 20.09 (2'-CH_3), 28.11 ($C(CH_3)_3$), 56.63 (C-1'), 81.90 ($C(CH_3)_3$), 111.49 (C-3'), 119.47 (C-3), 120.94 (C-5), 125.51, 127.65 (C-4, C-6), 130.90 (C-1), 141.20 (C-2'), 150.95 (C-2), 155.53 ($CO_2C(CH_3)_3$) ppm. **IR** (Pellet): $\tilde{\nu}$ = 3248, 2973, 1651, 1597, 1513, 1403, 1294 cm^{-1}. **UV** (CH_3CN): λ_{max} (lg ε) = 274.0 (3.395) nm. **MS** (ESI): m/z (%) = 549.3 (27) $[2\,M+Na]^+$, 302.12 (100) $[M+K]^+$, 286.14 (37) $[M+Na]^+$. Calcd for **$C_{15}H_{21}NO_3$**: 286.14136 $[M+Na]^+$. Found: 286.14146 $[M+Na]^+$ (ESI-HRMS).

Domino Wacker-Heck Reaction

(*rac*)-(*E*)-5-(2-Methyl-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)-pent-3-en-2-one ((*rac*)-31) : According to

general procedure **C**, phenol (**10**) (53.1 mg, 323 µmol) was reacted with methyl vinyl ketone (**27**) (45.3 mg, 647 µmol, 52.7 µL, 2.0 eq.), *p-b*enzoquinone (140 mg, 1.29 mmol, 4.0 eq.) and palladium trifluoroacetate (10.8 mg, 32.3 µmol, 0.1 eq.) in CH_2Cl_2 (0.35 mL) at room temperature for 10 h. Purification by column chromatography on silica (P/EtOAc = 5:1) yielded (*rac*)-**31** (66.2 mg, 285 µmol, 88 %) as a yellow oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, 2'-CH_3), 2.26 (s, 3 H, 1-H_3), 2.48 (ddd, J = 14.4, 8.3, 1.2 Hz, 1 H, 5-H_a), 2.65 (ddd, J = 14.5, 7.1, 1.5 Hz, 1 H, 5-H_b), 3.87 (d, J = 11.3 Hz, 1 H, 3'-H_a), 3.96 (d, J = 11.3 Hz, 1 H, 3'-H_b), 6.14 (dt, J = 15.9, 1.4 Hz, 1 H, 3-H), 6.76–6.93 (m, 5 H, 4-H, Ar-H) ppm. **^{13}C-NMR** (75.6 MHz, $CDCl_3$): δ = 21.37 (2'-CH_3), 27.08 (C-1), 38.81 (C-5), 70.43 (C-2'), 73.63 (C-3'), 117.00, 117.57 (C-5', C-8'), 121.22, 122.02 (C-6', C-7'), 134.64 (C-3), 141.26 (C-4), 141.97, 142.08 (C-4'a, C-8'a), 198.05 (C-2) ppm. **IR** (Film): $\tilde{\nu}$ = 2980 (C–H), 1674, 1630, 1593, 1494, 1362, 1264, 1201 cm^{-1}. **UV** (CH_3CN): λ_{max} (lg ε) = 200.0 (4.719), 217.5 (4.329), 278.0 (3.507), 331.0 (2.419) nm. **MS** (EI, 70 eV): m/z (%) = 232 (30) $[M]^+$, 149 (100) $[M–C_5H_7O]^+$. Calcd for **$C_{14}H_{16}O_3$**: 233.11722 $[M+H]^+$. Found: 233.11711 $[M+H]^+$ (ESI-HRMS).

(*rac*)-(*E*)-4-(2-Methyl-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)-but-2-enoic acid methyl ester ((*rac*)-32): Phenol (**10**) (49.8 mg, 303 µmol) was reacted with methyl acrylate (**28**) (52.2 mg, 607 µmol, 55.0 µL, 2.0 eq.), *p*-benzoquinone (131 mg, 1.21 mmol, 4.0 eq.) and palladium trifluoroacetate (10.1 mg, 30.3 µmol, 0.1 eq.) in CH_2Cl_2 (0.35 mL) at room temperature for 12 h following general procedure **C**. Purification by column chromatography on silica (P/EtOAc = 6:1) yielded (*rac*)-**32** (66.1 mg, 266 µmol, 88 %) as a colorless oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, 2'-CH_3), 2.48 (ddd, J = 14.4, 8.3, 1.3 Hz, 1 H, 4-H_a), 2.60 (ddd, J = 14.2, 7.2, 1.6 Hz, 1 H, 4-H_b), 3.74 (s, 3 H, OMe), 3.85 (d, J = 11.3 Hz, 1 H, 3'-H_a), 3.96 (d, J = 11.3 Hz, 1 H, 3'-H_b), 5.92 (dt, J = 15.7, 1.4 Hz, 1 H, 2-H), 6.79–6.92 (m, 4 H, Ar-H), 7.00 (ddd, J = 15.6, 8.2, 7.2 Hz, 1 H, 3-H) ppm. **^{13}C-NMR** (75.6 MHz, $CDCl_3$): δ = 21.23 (2'-CH_3), 38.48 (C-4), 51.54 (OMe), 70.28 (C-2'), 73.58 (C-3'), 116.95, 117.64 (C-5', C-8'), 121.13, 121.98 (C-6', C-7'), 124.81 (C-2), 141.98, 142.07 (C-4'a, C-8'a), 142.61 (C-3), 166.38 (C-2) ppm. **IR** (Film): $\tilde{\nu}$ = 2981, 1724, 1659, 1594, 1494, 1436, 1264 cm^{-1}. **UV** (CH_3CN): λ_{max} (lg ε) = 201.0 (4.720), 277.5 (3.472) nm. **MS** (EI, 70 eV): m/z (%) = 248 (24) $[M]^+$, 149 (100) $[M–C_5H_7O_2]^+$. Calcd for **$C_{14}H_{16}O_4$**: 249.11214 $[M+H]^+$. Found: 249.11214 $[M+H]^+$ (ESI-HRMS).

(*rac*)-(*E*)-2-Methyl-2-(4-oxopent-2-enyl)-2,3-dihydrobenzo[*b*][1,4]oxazin-4-carboxylic acid-*tert*-butyl ester ((*rac*)-66): Following general procedure **C**, phenol (**65**) (100 mg, 380 µmol) was converted with methyl vinyl ketone (**27**) (53.2 mg, 759 µmol, 61.9 µL, 2.0 eq.), *p*-benzoquinone (164 mg, 1.52 mmol, 4.0 eq.) and palladium trifluoroacetate (12.6 mg, 38.0 µmol, 0.1 eq.) in CH_2Cl_2 (0.40 mL) at 40 °C within 12 h. Purification by column chromatography on silica (P/EtOAc = 10:1) yielded (*rac*)-**66** (104 mg, 314 µmol, 83 %) as a yellow oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, 2-CH_3), 1.54 (s, 9 H,

$C(CH_3)_3$), 2.26 (s, 3 H, 5'-H_3), 2.47 (ddd, J = 14.3, 7.8, 1.3 Hz, 1 H, 1'-H_a), 2.55 (ddd, J = 14.3, 7.4, 1.3 Hz, 1 H, 1'-H_b), 3.57 (d, J = 13.6 Hz, 1 H, 3-H_a), 3.73 (d, J = 13.6 Hz, 1 H, 3-H_b), 6.14 (dm_c, J = 16.0 Hz, 1 H, 3'-H), 6.76–6.92 (m, 3 H, 2'-H, 6-H, 8-H), 7.00 (ddd, J = 7.6, 6.9, 1.5 Hz, 1 H, 7-H), 7.71 (s, 1 H, 5-H) ppm. **^{13}C-NMR** (75.6 MHz, $CDCl_3$): δ = 22.44 (2-CH_3), 26.91 (C-5'), 28.13 ($C(CH_3)_3$), 40.20 (C-1'), 49.15 (C-3), 75.51 (C-2), 81.68 ($C(CH_3)_3$), 117.19, 119.91 (C-6, C-8), 123.40 (C-5), 124.61 (C-7), 124.69 (C-4a), 134.48 (C-3'), 141.53 (C-2'), 144.95 (C-8a), 152.76 ($CO_2C(CH_3)_3$), 197.96 (C-4') ppm. **IR** (Film): $\tilde{\nu}$ = 2974, 1696, 1674, 1377, 1252 cm^{-1}. **UV** (CH_3CN): λ_{max} (lg ε) = 211.5 (4.666), 282.5 (3.556) nm. **MS** (EI, 70 eV): m/z (%) = 331.2 (22) $[M]^+$, 231.2 (78) $[M–C_5H_9O_2]^+$, 148.1 (44) $[M–C_{10}H_{16}O_3]^+$. Calcd for **$C_{19}H_{25}NO_4$**: 370.14152 $[M+K]^+$. Found: 370.14146 $[M+K]^+$ (ESI-HRMS).

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie. We thank DSM-Vitamins for reference samples and Symrise for supplying (R)-citronellol. F.S. thanks the Deutsche Bundesstiftung Umwelt (DBU) for a Ph.D. scholarship.

REFERENCES

1. a) L. F. Tietze, G. Brasche, and K. M. Gericke, "*Domino Reactions in Organic Synthesis*", Wiley-VCH, Weinheim, 2006. b) L. F. Tietze, H. Ila, and H. P. Bell, *Chem. Rev.*, 2004, **104**, 3453. c) L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304. d) L. F. Tietze and F. Haunert in *Stimulating Concepts in Chemistry* (Ed.by F. Vögtle, J. F. Stoddart, and M. Shibasaki, Wiley-VCH, Weinheim, 2000, pp. 39–64. e) L. F. Tietze and M. E. Lieb, *Curr. Opin. Chem. Biol.*, 1998, **2**, 363. f) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115. g) L. F. Tietze and U. Beifuss, *Angew. Chem.*, 1993, **105**, 137; *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131. h) A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945. i) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009. j) A. de Meijere and E. F. Meyer in *Metal-catalyzed Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, 1998. k) M. Beller, T. H. Riermeir, and G. Stark in *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 1998.
2. a) L. F. Tietze, K. M. Sommer, J. Zinngrebe, and F. Stecker, *Angew. Chem.*, 2005, **117**, 262; *Angew. Chem. Int. Ed.* 2005, **44**, 257. b) L. F. Tietze, F. Stecker, J. Zinngrebe, and K. M. Sommer, *Chem. Eur. J.*, 2006, *in press*.
3. a) H. Hocke and Y. Uozumi, *Synlett*, 2002, 2049. b) T. Furutani, M. Hatsuda, R. Imashiro, and M. Seki, *Tetrahedron: Asymmetry*, 1999, **10**, 4763. c) F. Dubois and M. Gingras, *Tetrahedron Lett.*, 1998, **39**, 5039. d) Y. Uozumi, K. Kato, and T. Hayashi, *J. Am. Chem. Soc.*, 1997, **119**, 5063. e) M. B. Andrus, D. Asgari, and J. A. Sclafani, *J. Org. Chem.*, 1997, **62**, 9365. f) Y. Uozumi, H. Kyota, E.

Kishi, K. Kitayama, and T. Hayashi, *Tetrahedron: Asymmetry*, 1996, **7**, 1603. g) T. D. Nelson and A. I. Meyers, *J. Org. Chem.*, 1994, **59**, 2655. h) J.-I. Kim and G. B. Schuster, *J. Am. Chem. Soc*., 1992, **114**, 9309. i) A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, 1984, **40**, 1245.

4. V. B. Deodhar, V. S. Dalavoy, and U. R. Nayak, *Org. Prep. Proc. Int.*, 1993, **25**, 583.
5. K. Kitaori, Y. Furukawa, H. Yoshimoto, and J. Otera, *Adv. Synth. Catal.*, 2001, **343**, 95.
6. a) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285. b) C. Hyland, *Tetrahedron*, 2005, **61**, 3457. c) J. Barluenga and C. Valdés, *Chem. Commun*., 2005, 4891. d) M. Massacret, P. Lhoste, and D. Sinou, *Eur. J. Org. Chem.*, 1999, 129. e) L. Hegedus and J. M. Kearin, *J. Am. Chem. Soc.*, 1982, **104**, 2444.