68. A Short Synthesis of the Factor-Xa Inhibitor DX-9065a Using Palladium-Catalyzed Key Steps[1])

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Dedicated to Professor Dr. *Rolf Gleiter*, Heidelberg, on the occasion of his 60th birthday with best wishes

(27.I.97)

We describe a new, efficient synthesis of DX-9065a (**4**), a potent inhibitor of the blood coagulation enzyme factor Xa (fXa) which has previously been prepared in more than 20 steps. We saved approximately 10 steps starting with a Pd-catalyzed cyanation of the triflate **10** of 7-methoxynaphthalen-2-ol (**9**). After cleavage of the MeO group with boron tribromide, the triflate **6** was coupled to acrylate **5** in a *Heck* reaction (→ **3**). The subsequent transformations led to DX-9065a.

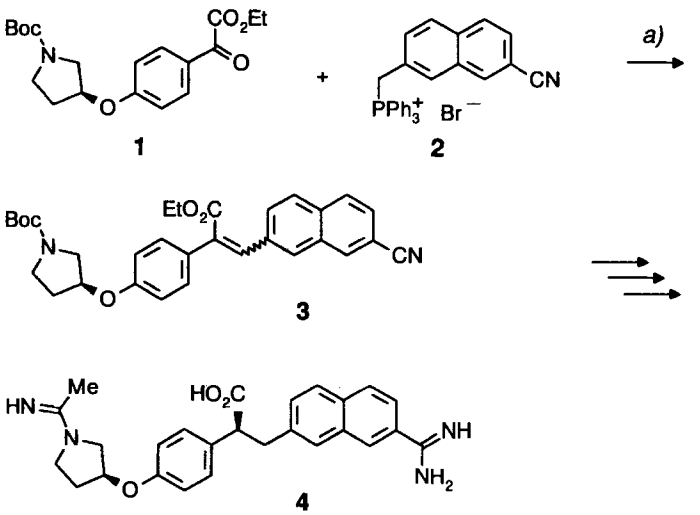
Introduction. – The selective inhibition of the blood coagulation enzyme factor Xa (fXa) represents an attractive target for anticoagulant therapy because fXa occupies a strategic location at the intersection of the extrinsic and the intrinsic blood coagulation pathways [1]. Recently, some of us solved the structure of the complex of fXa and DX-9065a (**4**) [2], the first orally active fXa inhibitor [3]. The 2-amidinonaphthalene (= 2-carbaminidoylnaphtalene) moiety (P1 residue) of **4** is bonded in the recognition site (S1 site), and the acetimidoyl group (P4) is located in the 'cation hole' [2] (S4 site), part of which forms during inhibitor binding (induced fit)[2]). The 2,7-disubstitution pattern of the naphthalene moiety of **4** allows the simultaneous occupation of the two sites. The preparation of suitable 2,7-disubstituted naphthalene derivatives is demanding: more than 20 steps were necessary for the synthesis of **4** from **1** and **2** *via* **3** [5] (*Scheme 1*), the major part (11 steps) being required by the *Haworth* synthesis [6] of the naphthalene derivative **2** starting from toluene. We planned to develop a new route to DX-9065a (**4**). Our objective was in particular to reduce the number of steps of the synthesis of the naphthalene derivative. It was envisioned that the crucial intermediate **3** could also be obtained by a *Heck* reaction of acrylate **5** and naphthalenyl triflate **6** (*Scheme 2*).

Results and Discussion. – The route to **3** *via* a *Heck* reaction of **6** should be much shorter than the published one [5] since a four-step synthesis for the naphthalenol

[1]) Part of the Ph. D. Thesis of *C. Kehr*, University of Heidelberg, 1996.

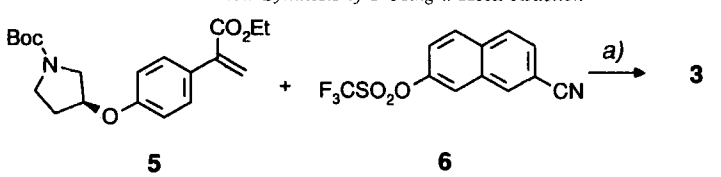
[2]) This follows from the comparison of the X-ray structure of the complex with that of uninhibited fXa [4].

Scheme 1. *Published* [5] *Synthesis of the Precursor* **3** *of DX-9065a* (**4**)



a) DBU, EtOH/THF.

Scheme 2. *New Synthesis of* **3** *Using a* Heck *Reaction*

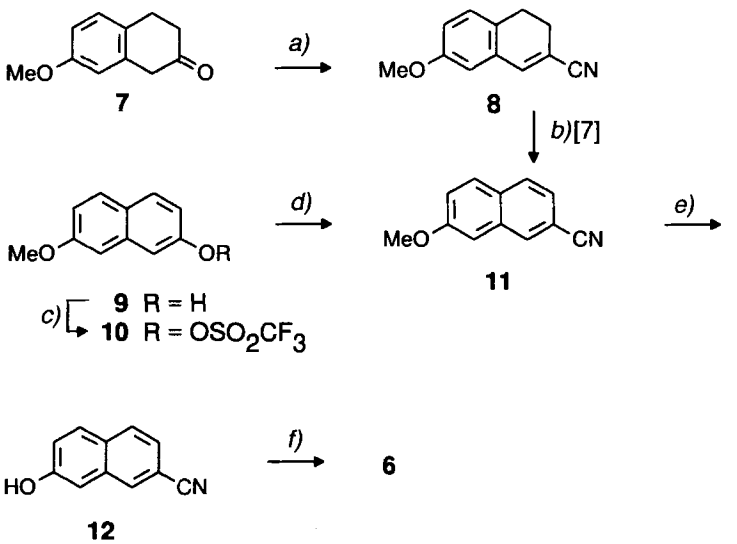


a) Et_3N, *trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II) (2.5 mol-%), DMF, 120°, 32 h (43%).

precursor **12** of **6** starting from the tetralone **7** is known [7] (*Scheme 3*). However, no yields for the intermediate dihydronaphthalenecarbonitrile **8** were reported. Using the described procedure, *i.e.*, BH_3-catalyzed reaction of **7** with trimethylsilyl cyanide [7], we isolated only 19% of **8**. This low yield may be due to the high carbonyl activity of tetralone **7** favoring its auto-aldol condensation.

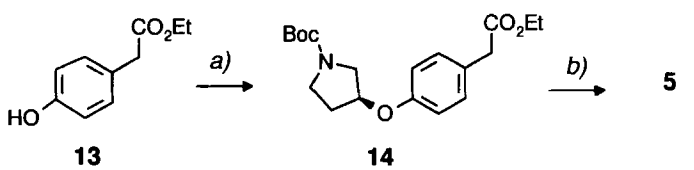
Because of these difficulties, we explored the feasibility of using as starting material the low-priced naphthalene-2,7-diol derivative **9** (*Scheme 3*). Indeed, an elegant $[Pd(PPh_3)_4]$-catalyzed conversion of aryl halides into aryl cyanides by $Zn(CN)_2$ is known [8], and a first conversion involving an aryl triflate was reported recently [9] which might be applied to triflate **10** derived from **9**. This proved to be a viable strategy. The conversion of triflate **10** by $Zn(CN)_2$ into nitrile **11** was readily completed in the presence of $Pd(OAc)_2$. The best results were obtained by adding $Pd(OAc)_2$ to a heated (150°) suspension of $Zn(CN)_2$, **10**, and PPh_3 in 1-methylpyrrolidin-2-one. Precipitation of Pd occurred quickly and was essential for the conversion of **10**. The reaction was neither catalyzed by 10% Pd/C nor by the heat-stable palladacycle which was recently introduced by *Herrmann*, *Beller*, and coworkers [10]. The MeO group of **11** can be split by NaCN in DMSO at high temperature [7]: However, to avoid the HCN gas production

Scheme 3



a) 1. Me_3SiCN, BF_3OEt_2, 60°; 2. $POCl_3$, pyridine (19%). *b)* S_8, 10% Pd/C [7]. *c)* $PhN(SO_2CF_3)_2$, Et_3, (90%). *d)* $Zn(CN)_2$, PPh_3, $Pd(OAc)_2$ (5 mol-%). 1-methylpyrrolidin-2-one 150–160° (86%). *e)* BBr_3, CH_2Cl_2 (88%). *f)* $PhN(SO_2CF_3)_2$, Et_3N (99%).

Scheme 4



a) tert-Butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate, DEAD, PPh_3, THF, r.t. (85%). *b)* HCHO, K_2CO_3, Bu_4NI, toluene, 80–90° (84%).

caused by the acidic workup of the reaction mixture, we preferred the cleavage of methyl ether **11** with BBr_3 at room temperature (→ **12**). Subsequently, hydroxynaphthalenecarbonitrile **12** was converted to triflate **6**, the starting material for the planned *Heck* reaction.

Acrylate **5** was prepared by a *Mitsunobu* reaction of *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate and phenol **13** followed by a phase-transfer-catalyzed condensation with formaldehyde (*Scheme 4*). The *Heck* reaction of triflate **6** and acrylate **5** was then carried out in the presence of the stable palladacycle [10] which tolerated the high reaction temperature (120°) and prolonged reaction time (32 h) without decomposition (*Scheme 2*). We obtained the desired olefin **3** as a 2:1 mixture of (*E*/*Z*) isomers. From the intermediate **3** we prepared DX-9065a (**4**) according to the published procedures [5].

Thus, new route starting from the commercially available naphthalene-2,7-diol derivative **9** and ethyl 4-hydroxyphenylacetate (**13**) allows a much shorter synthesis of DX-9065a (**4**). The key steps are the introduction of the C-substituent at the naph-

thalene moiety, using a Pd-catalyzed coupling reaction and the easy conversion of a hydroxy into a nitrile group. These steps greatly facilitate the preparation of 7-substituted naphthalene-2-carboximidanides (= 2-naphthamidines) and, therefore, of new fXa inhibitors[3]) for the use in structure-based anticoagulant research [12]. Further work in this direction is in progress.

We thank *Boehringer Mannheim GmbH*, *BASF AG*, *Bayer AG*, *Hoechst AG*, the *Fonds der Chemischen Industrie*, and the *Deutsche Forschungsgemeinschaft* for support of this work. We would also like to thank Dr. *U. Anders*, *W. Ehleiter*, and *S. Laukenmann* for NMR spectra, Dr. *H. Hindermayer* for mass spectra, *I. Braun*, *S. Braun*, *K. Marschar*, *H. Treiber*, *R. Sieveritz*, Dr. *I. Brodowsky*, and *H. Rudy* for elemental analyses and IR spectra, and *A. Teuscher* and *R. Wetzel* for technical assistance.

Experimental Part

General. The reactions were carried out under N_2 in degassed solvents. Standard workup procedure: Addition of H_2O, extraction with AcOEt, washing the org. phase with brine, drying (Na_2SO_4), and evaporation. Column chromatography (CC): silica gel (0.063–0.2 mm, *Merck*). M.p.: *SG 01* (*HWS*): uncorrected. IR Spectra: *IFS 48* (*Bruker*): KBr pellets; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: AC 250 (*Bruker*); ^1H, 250 MHz, $(D)_6DMSO$, $SiMe_4$; ^{13}C, 63 MHz, $(D)_6DMSO$, $SiMe_4$; ^{19}F, 235 MHz, $(D)_6DMSO$, external $CFCl_3$; δ in ppm, J in Hz. MS: *MAT 312* (*Finnigan*), 70 eV; *m/z* (rel. %). Elemental analyses: Elemental analyzer *1106* (*Carlo Erba*).

tert-*Butyl (S)-3-{4-[2-(7-Cyanonaphthalen-2-yl)-1-(ethoxycarbonyl)ethenyl]phenoxy}pyrrolidine-1-carboxylate* (**3**). *trans*-Di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) [10] (0.6 g, 0.6 mmol) was added to a soln. of **6** (7.20 g, 24.0 mmol), **5** (8.70 g, 24.0 mmol), and Et_3N (6.70 ml, 48.0 mmol) in DMF (200 ml). After stirring for 16 h at 120°, catalyst (0.6 g) was added again, and the suspension was stirred for 16 h at 120°. After standard workup the brown oil (30 g) was purified by CC (isohexane/AcOEt 95:5 → 70:30): 5.30 g (43%) of **3**. Colorless viscous oil. ^1H-NMR: consistent with those reported [5]; (*E*/*Z*) ratio 2:1, by integration of the signals of H–C(8) (naphth.) and of Et.

tert-*Butyl (S)-3-{4-[1-(Ethoxycarbonyl)ethenyl]phenoxy}pyrrolidine-1-carboxylate* (**5**). A mixture of **14** (14.0 g, 40.0 mmol), paraformaldehyde (1.80 g, 60.0 mmol), K_2CO_3 (8.90 g, 64.0 mmol), and Bu_4NI (0.3 g, 0.8 mmol) in toluene (300 ml) was heated to 80–90° for 40 h. Standard workup yielded 12.1 g (84%) of **5**. Colorless viscous oil. IR: 2977*m*, 2937*w*, 2883*w* (C–H), 1734*s* (EtOC=O), 1695*s* (N–C=O), 1613*w*, 1510*s* (C=C), 1479*w*, 1403*s*, 1366*s*, 1297*w*, 1237*s* (C–O), 1165*s*, 1116*m*, 1032*s*. ^1H-NMR: 1.26 (*t*, ^3J = 7.2, Me); 1.39 (*s*, *t*-Bu); 1.96–2.16 (*m*, 2H); 3.25–3.64 (*m*, 4H); 4.21 (*q*, ^3J = 7.2, CH_2O); 5.02 (*m*, 1H); 5.93 (*s*, 1H, $=CH_2$); 6.12 (*s*, 1H, $=CH_2$); 6.93 (*d*, ^3J = 8.7, 2H); 7.36 (*d*, ^3J = 8.7, 2H). MS: 361(19, M^+), 70(68, $C_4H_8N^+$), 69(42, $C_4H_7N^+$), 57(100, $C_4H_9N^+$). Anal. calc. for $C_{20}H_{27}NO_5$ (361.44): C 66.46, H 7.53, N 3.88; found: C 66.24, H 7.61, N 3.80.

7-Cyanonaphthalene-2-yl Trifluoromethanesulfonate (**6**). In an ice bath, Et_3N (1.64 ml, 11.8 mmol) was added dropwise to a suspension of **12** (2.00 g, 11.8 mmol) und *N*,*N*-bis-[(trifluoromethyl)sulfonyl]aniline (4.64 g, 13.0 mmol) in CH_2Cl_2 (20 ml). Stirring for 2 h at r.t. followed by standard workup and filtration over SiO_2 (40 g, elution with Et_2O) yielded **6** (3.50 g, 99%) Colorless crystals. M.p. 77–79° (CH_2Cl_2/cyclohexane). IR: 3084*w*, (C–H), 2236*m*, (CN), 1609*w* (C=C), 1507*w* (C=C), 1415*s*, 1245*m*, 1223*m*, 1214*m*, 1142*m*, 1113*m*, 956*m*, 909*m*, 884*m*, 849*m*, 623*m*, 596*m*. ^1H-NMR: 7.82 (*dd*, ^3J(5, 6) = 9.2, ^4J(6, 8) = 2.4, H–C(6)); 7.92 (*dd*, ^3J(3, 4) = 8.5, ^4J(1, 3) = 1.6, H–C(3)); 8.21–8.33 (*m*, 3H); 8.71 (*s*, H–C(1)). ^{13}C-NMR: 110.36(C(2)); 118.33 (*q*, ^1J(C, F) = 321, CF_3); 118.56(CN); 120.13, 122.88, 127.83, 129.56, 131.45, 132.10, 133.42, 134.46(C(1)); 147.61(C(7)). ^{19}F-NMR: −72.28. MS: 301(29, M^+), 168(50, $[M - SO_2CF_3]^+$), (100, $[M - CO - SO_2CF_3]^+$). Anal. calc. for $C_{12}H_6F_3NO_3S$ (301.25): C 47.85, H 2.01, N 4.65, S 10.64; found: C 47.83, H 1.92, N 4.64, S 10.56.

3,4-Dihydro-7-methoxynaphthalene-2-carbonitrile (**8**). A mixture of **7** (*Aldrich*; 2.00 ml, 12.8 mmol), Me_3SiCN (1.76 ml, 14.1 mmol), and a catal. amount of $BF_3 \cdot Et_2O$ was stirred at 60° for 5 h. Pyridine (8.0 ml) and $POCl_3$ (2.7 ml) were added and the mixture evaporated. Iced water was given to the residue, followed by saturation with NaCl and extraction with Et_2O. The combined Et_2O extracts were washed with 2N HCl, brine, and dried (Na_2SO_4). Evaporation and CC (isohexane/AcOEt 80:20) yielded 440 mg (19%) of **8**. Colorless crystals. M.p. 71–73° ([13]: 72–73°).

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[3]) For improved fXa inhibitors bearing the 2,7-disubstituted naphthalene moiety, see [11].

7-Methoxynaphthalene-2-yl Trifluormethanesulfonate (**10**) was prepared from **9** (*Aldrich*; 8.86 g, 50.9 mmol) as described for **6**: 14.1 g (90%) of **10**. Colorless crystals. M.p. 34° ([14]: oil).

7-Methoxynaphthalene-2-carbonitrile (**11**). At 150°, $Pd(OAc)_2$ (750 mg, 3.34 mmol) was added to a suspension of **10** (20.5 g, 66.8 mmol), $Zn(CN)_2$ (4.71 g, 40.1 mmol) and PPh_3 (876 mg, 3.34 mmol) in 1-methylpyrrolidin-2-one (200 ml). Pd precipitated immediately. After 30 min at 160°, $Pd(OAc)_2$ (225 mg, 1.00 mmol) was added again, followed by 1 h stirring at 160°. Standard workup followed by the purification of the crude brown oil (33.3 g) by CC (SiO_2, isohexane/AcOEt 90:10 → 75:25) yielded 10.6 g (86%) of **11**. Colorless crystals. M.p. 81° ([13]: 85°).

7-Hydroxynaphthalene-2-carbonitrile (**12**). In an ice bath, a soln. of BBr_3 (8.4 ml, 88 mmol) in CH_2Cl_2 (40 ml) was added to a soln. of **11** (6.46 g, 35.3 mmol) in CH_2Cl_2 (60 ml). After 48 h at r.t. H_2O (80 ml) was added and the suspension filtered. The precipitate was washed with CH_2Cl_2 and purified further (see below). The aq. phase was extracted with CH_2Cl_2. The combined org. phases were extracted with 2N NaOH, the combined NaOH solns. were acidified with conc. HCl soln. and extracted with AcOEt. The precipitate (see above) was dissolved in AcOEt, and the combined org. layers were dried (Na_2SO_4) and evaporated: 5.27 g (88%) of **12**. Colorless crystals. M.p. 189–190° ([15]: 183–185°).

tert-*Butyl (S)-3-{4-[(Ethoxycarbonyl)methyl]phenoxy}pyrrolidine-1-carboxylate* (**14**). Ester **13** (11.2 g, 62.0 mmol), *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (11.6 g, 62.0 mmol), PPh_3 (20.4 g, 78.0 mmol), and diethyl diazenedicarboxylate (DEAD; 12.2 ml, 78.0 mmol) in THF (300 ml) were stirred at r.t. PPh_3 (2.0 g, 7.8 mmol), *tert*-butyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (1.2 g, 6.2 mmol) and DEAD (1.22 ml, 7.80 mmol) were again added after 16, 60, and 76 h. CC (isohexane/AcOEt 98:2 → 80:20) yielded 18.4 g (85%) of **14**. Yellow oil. IR: 2977*m*, 2937*w*, 2883*w* (C–H), 1734*s* (EtO–C=O), 1695*s* (N–C=O), 1613*w*, 1510*s* (C=C), 1479*w*, 1403*s*, 1366*s*, 1297*w*, 1237*s* (C–O), 1165*s*, 1116*m*, 1032*w*. ^{1}H-NMR: 1.18 (*t*, ^3J = 7.1, *Me*CH_2); 1.39 (*s*, *t*-Bu); 1.94–2.20 (*m*, CH_2); 3.23–3.60 (*m*, $2CH_2N$); 3.56 (*s*, ArCH_2); 4.96 (*m*, CH–O); 6.87 (*d*, ^3J = 8.5, 2H); 7.17 (*d*, ^3J = 8.5, 2H). MS (70 eV): 349(10, M^+), 107(47, $C_7H_7O^+$), 70(61, $C_4H_8N^+$), 69(55, $C_4H_7N^+$), 57(100, $C_4H_9^+$). Anal. calc. for $C_{19}H_{27}NO_5$ (349.43): C 65.31, H 7.79, N 4.01; found: C 65.05, H 7.95, N 4.29.

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