A Thymine-PNA Monomer as New Isocyanide Component in the Ugi Reaction: A Direct Entry to PNA Dimers

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Abstract: A new PNA monomer was synthesized for use as the isocyanide component in a Ugi condensation in order to produce peptide nucleic acid (PNA) dimers also labelled with $Cr(CO)_3$.

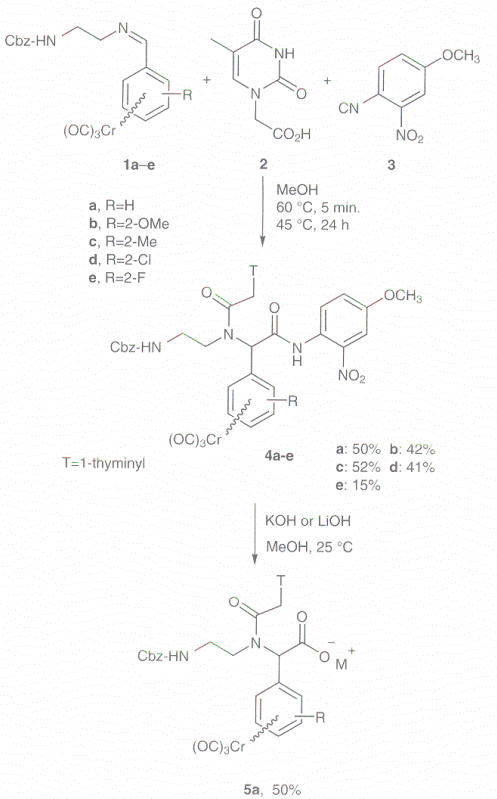
Key words: multicomponent reaction, arene complexes, chromiumtricarbonyl, peptide nucleic acid, isocyanide

The Ugi four-component reaction (U-4CR)[1] is a very efficient approach to the synthesis of peptides[2] and peptide nucleic acid (PNA)[3,4] monomers. An interesting novel application of this strategy has been reported by Dömling,[5] who used *N*-Boc-aminoethylisocyanide as the isocyanide component in the Ugi condensation in order to produce highly versatile monomeric PNA building blocks also in a combinatorial manner.

In a recent paper,[6] we described the use of the Ugi reaction to synthesize a series of chiral racemic $ArCr(CO)_3$ labelled PNA monomers **4a–e**[7] bearing the organometallic moiety linked to the α-carbon of the glycine unit (Scheme 1).[8] The unique chemical and spectroscopic properties of organometallic complexes can be exploited in PNAs as a means of comparing various biological and diagnostic issues, such as the improvement of lipophilicity and the direct detection of a labelled biomolecule.[9,10] The next step in this study is to use complexed monomers **4** to obtain multi-labelled PNA oligomers. The synthesis is usually performed on solid phase[11] by elongating the chain first from the side of the glycine carboxy group. A crucial aspect of this process is the efficient hydrolysis of the amide group in monomers **4a–e**. The isocyanide **3** was specifically chosen because the corresponding 4-methoxy-2-nitro-phenyl amide can be hydrolyzed under basic conditions,[4] that are compatible with the $Cr(CO)_3$ group. We here describe our experiments for hydrolyzing the 4-methoxy-2-nitro-phenylamide in monomers **4a–e**, and how the problem of the degradation of the *ortho*-substituted substrates found in this reaction was overcome by using a new isocyanide component in the Ugi reaction.

As reported in our previous paper,[6] hydrolysis of the α-phenyl $Cr(CO)_3$ substituted monomer **4a** using 1.5 equivalents of LiOH or KOH gave **5a** in 50% yield after 24 hours at room temperature (Scheme 1). The same reaction was surprisingly unsuccessful when extended to the *ortho*-substituted complexed monomers **4b–e** as well as the hydrolysis of **4b–e** (as single diastereoisomers) for 24 hours with 1.5 equivalents of LiOH or KOH led to the complete epimerization of the monomers, without any trace of the corresponding acids. Increasing the base amount (up to 6 equiv) or the temperature (up to 45 °C) only caused the degradation of monomers **4b–e**.

Because of these unexpected results, for the sake of comparison, we then tried hydrolysing (with KOH or LiOH) the corresponding uncomplexed monomers. Comparable



Scheme 1 Ugi reaction on benzaldimine $Cr(CO)_3$ complexes

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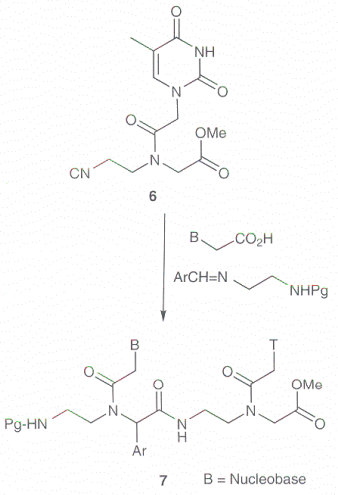
results were obtained: the reaction only took place in the case of the phenyl substituted compound,[6] whereas just stirring the *ortho*-substituted monomers at room temperature led to their decomposition.[12]

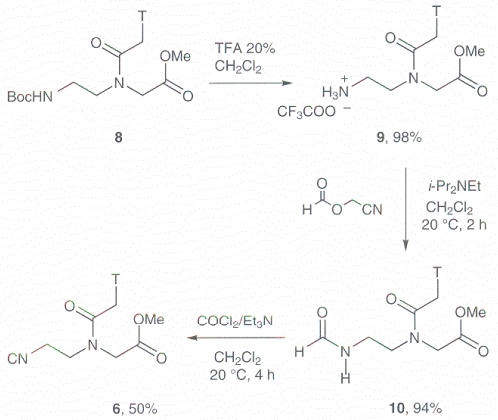
Although a number of hydrolysis conditions are currently being investigated, in order to overcome this serious drawback to the elongation of the PNA chain on these monomers, we decided to use the new isocyanide PNA monomer derivative **6** (Scheme 2) as the isocyanide component in the Ugi reaction. In this way, the Ugi reaction of the isocyanide monomer **6** with benzaldimine complexes and different 1-carboxymethylnucleobases should in principle lead directly to a series of PNA dimers **7** (Scheme 2).[13]



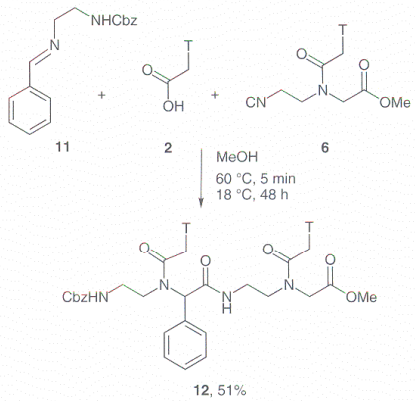
Scheme 2 Use of the new isocyanide **6** in the Ugi condensation to give PNA dimers

The new isocyanide **6** was synthesized as shown in Scheme 3. The starting material was the *N*-Boc protected thymine-PNA monomer **8**, which was synthesized as previously reported in the literature.[14] Treatment of **8** with a 20% solution of CF_3CO_2H in CH_2Cl_2 at room temperature gave **9** as a trifluoroacetate salt in quantitative yield. This was easily *N*-formylated using cyanomethyl formate[15] in CH_2Cl_2 at room temperature, and afforded **10** in 94% yield as a stable white solid.[16] The *N*-formyl monomer **10** was then dehydrated with $COCl_2/Et_3N$ in CH_2Cl_2[17] at room temperature to give after column chromatography isocyanide PNA monomer **6** in 50% yield, as a stable white solid.[18]

Isocyanide **6** was then tested in an Ugi condensation with uncomplexed benzaldimine **11** and carboxymethyl thymine **2** (Scheme 4).



Scheme 3 Synthesis of isocyanide PNA monomer **6**

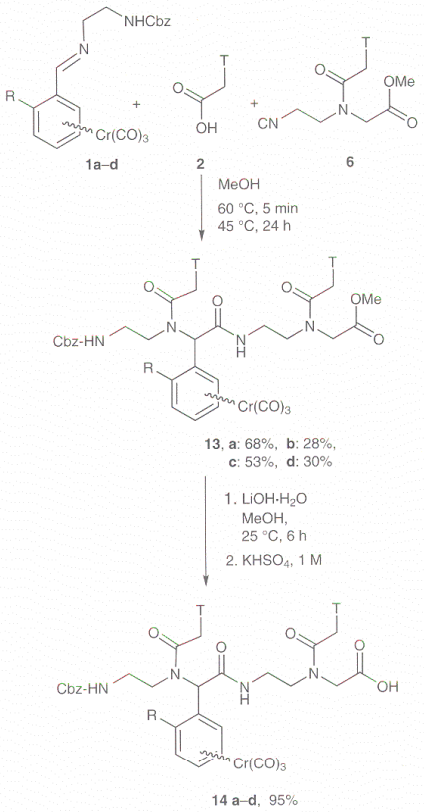


Scheme 4 Ugi condensation to give uncomplexed PNA dimer

An equimolar mixture of the three reagents was heated for 5 minutes at 60 °C and then stirred at room temperature for 48 hours. A standard work-up followed by chromatographic separation gave the PNA dimer **12**[19] in 51% yield.

The reaction was repeated on benzaldimine complexes **1a–d** (Scheme 5): in this case, the mixture was heated in MeOH for 24 hours at 45 °C. Column chromatography separation gave the new complexed PNA dimers **13a–d** in 28–68% yield.[20] Chiral dimers **13b–d** were obtained as a mixture of the two diastereoisomers in a 1:1 ratio.

Finally, in order to verify the possibility of constructing a PNA oligomer, we tried hydrolysis of the methyl ester in compounds **13a–d**: their treatment with 5 equivalents of LiOH in MeOH at 25 °C afforded the corresponding acids **14a–d**[21] in almost quantitative yields.



Scheme 5 Ugi condensation to give $Cr(CO)_3$-labelled PNA dimers

In conclusion we have shown that the use of the new isocyanide **6**, in the Ugi condensation, allows to successfully circumventing the problem of the carboxamide hydrolysis in 2-substituted complexed and uncomplexed aryl-PNA monomers. These results clearly candidate PNA monomer **6** as an effective tool for the synthesis of different dimers, also in a combinatorial manner. Our current studies include the synthesis of a $Cr(CO)_3$ complexed isocyanide PNA monomer in order to obtain dimers containing two organometallic units.

Acknowledgment

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References

(1) (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. (c) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306. (d) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2086. (e) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (f) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (g) Henkel, B.; Sax, M.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 7015. (h) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021.

(2) (a) Shibata, N.; Kumar Das, B.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 197. (b) Kazmaier, U.; Hebach, C. *Synlett* **2003**, 1591. (c) Ziegler, T.; Gerlin, S.; Lang, M. *Angew Chem. Int. Ed.* **2000**, *30*, 2109.

(3) (a) Nielsen, P. E.; Egholm, M. *Peptide Nucleic Acids. Protocols and Applications*; Horizon Scientific Press: Wymondham, Norfolk, UK, **1999**. (b) Antsypovitch, S. I. *Russ. Chem. Rev.* **2002**, *71*, 71. (c) Irgolic, K. J. In *Houben-Weyl*, 4th ed., Vol. E12b; Klamann, D., Ed.; Thieme: Stuttgart, **1990**, 150.

(4) (a) Maison, W.; Schlemminger, I.; Westerhoff, O.; Martens, J. *Bioorg. Med. Chem. Lett.* **2000**, *8*, 1343. (b) Shibata, N.; Das, B. K.; Honjo, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1605.

(5) (a) Dömling, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2871. (b) The same reaction was recently repeated by: Xu, P.; Zhang, T.; Wang, W.; Zou, X.; Zhan, X.; Fu, Y. *Synthesis* **2003**, 1171.

(6) Baldoli, C.; Maiorana, S.; Licandro, E.; Zinzalla, G.; Perdicchia, D. *Org. Lett.* **2002**, *24*, 4341.

(7) For compounds **4a-d** see ref.[6]; compound **4e**: yield: 15%, 60:40 diastereoisomeric ratio; Diast. I: R_f = 0.51 (EtOAc). Mp 142 °C dec. (pentane). Anal. Calcd for $C_{35}H_{31}CrFN_6O_{12}$: C, 52.64; H, 3.91; N, 10.52. Found: C, 52.70; H, 3.88; N, 10.50. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (s, 3 H, CH_3), 3.36–3.54 (m, 2 H, NCH_2CH_2N), 3.82 (s, 3 H, OCH_3), 3.88–4.13 (m, 3 H, $NCH_2CH_2N + CH_2CO$), 4.69 (s, 1 H, CH), 4.74–4.79 (m, 1 H, CH_2CO), 4.92–5.05 [m, 3 H, $PhCr(CO)_3 + CH_2O$], 5.30–5.39 [m, 1 H, $PhCr(CO)_3$], 5.43 [dd, 1 H, $J_1 = J_2$ = 6.1 Hz, $PhCr(CO)_3$], 5.73 (s, 1 H, NH), 6.01 [m, 2 H, $PhCr(CO)_3$], 6.50 (s, 1 H, CH=), 7.19 (dd, 1 H, *J* = 2.4, 9.0 Hz, arom.), 7.28–7.42 (m, 5 H, Ph), 7.60 (d, 1 H, *J* = 2.4 Hz, arom.), 8.30 (s, 1 H, NH), 8.59 (d, 1 H, *J* = 9.0 Hz, arom.), 10.51 (s, 1 H, NH). IR (nujol): 1967, 1905, 1881, 1692–1672 cm^{-1}. Diast. II: R_f = 0.31 (EtOAc), eluted as a mixture of complexed and uncomplexed monomer. ^{1}H NMR ($CDCl_3$): δ = 1.80 (s, 3 H, CH_3), 3.34–3.46 (m, 4 H, NCH_2CH_2N), 3.83 (s, 3 H, OCH_3), 4.43–4.55 (m, 3 H, CH_2CO + CH), 5.08–5.11 [m, 4 H, $PhCr(CO)_3 + CH_2O$], 5.84–5.93 [m, 3 H, $PhCr(CO)_3$ + NH], 6.70 (s, 1 H, CH=), 7.05–7.62 (m, 7 H, Ph + arom.), 8.56 (s broad, 2 H, arom. + NH), 10.54 (s, 1 H, NH). IR (nujol): 1975, 1894, 1680 cm^{-1}.

(8) For the effect on binding properties of substituents at glycine α-carbon in PNA oligomers see: Püschl, A.; Sforza, S.; Haaima, G.; Dahl, O.; Nielsen, P. E. *Tetrahedron. Lett.* **1998**, *39*, 4707.

(9) (a) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem. Int. Ed.* **1998**, *37*, 1634. (b) Jaouen, G.; Salmain, M.; Vessieres, A.; Varenne, A.; Brossiers, P. *J. Organomet.Chem.* **1999**, *589*, 92. (c) Metzler-Nolte, N. *Angew. Chem. Int. Ed.* **2001**, *40*, 1040. (d) Metzler-Nolte, N.; Verheijen, J. C.; van der Marel, G.; van Boom, J. H. *Bioconjugate Chem.* **2000**, *11*, 741. (e) Metzler-Nolte, N.; van Staveren, D. R. *Chem. Commun.* **2002**, 1406. (f) Baldoli, C.; Maiorana, S.; Licandro, E.; Vandoni, B.; Perdicchia, D.; Giannini, C.; Salmain, M. *J. Mol. Catal. A: Chem.* **2003**, *203-204*, 165.

(10) The use of a Ugi condensation to obtain tungsten carbonyl complexes of amino acids has been recently reported : Kernbach, U.; Mühl, M.; Polborn, K.; Fehlammer, W. P.; Jaouen, G. *Inorg. Chim. Acta* **2002**, *334*, 45.

(11) Corradini, R.; Nielsen, P.; Tedeschi, T.; Marchelli, R.; Pushl, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1629.

(12) Further experiments are in progress in order to rationalize this behaviour and clarify the role of the substituent, using a series of *meta*-substituted complexed and uncomplexed monomers.

(13) The synthesis of isocyano dipeptides has been recently reported: Zhao, G.; Bughin, C.; Bienaymé, H.; Zhu, J. *Synlett* **2003**, 1153.

(14) Uhlmann, E.; Peyman, A.; Breipohl, G.; Will, D. W. *Angew. Chem. Int. Ed.* **1998**, *37*, 2796.

(15) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H.-J. *Synthesis* **1996**, 37.

(16) Compound **10**: The trifluoroacetate salt **9** (3.0 mmol) and cyanomethyl formate (3.0 mmol) were dissolved in CH_2Cl_2 (25 mL) and cooled in an ice-bath to 0 °C. Then, a solution of DIEA (3.66 mmol) in CH_2Cl_2 (5 mL) was added. The solution was stirred for 2 h at 20 °C. After evaporation of the solvent, the crude product was purified by column chromatography (eluent: EtOAc:MeOH, 6:4, R_f = 0.36) affording compound **10**, as white solid, in 94% yield. Mp 62–63 °C (pentane). Anal. Calcd for $C_{13}H_{18}N_4O_6$ (326.3): C, 47.85; H, 5.56; N, 17.17. Found: C, 47.98; H, 5.54; N, 17.17. ^{1}H NMR (300 MHz, CD_3OD) two rotamers I/II in a 60:40 ratio are present: δ = 1.87 (s, 3 H, CH_3), 3.34–3.72 (m, 4 H, NCH_2CH_2), 3.72 (s, 3 H, OCH_3, I rot.), 3.80 (s, 3 H, OCH_3, II rot.), 4.14 (s, 2 H, NCH_2COOCH_3, I rot.), 4.34 (s, 2 H, NCH_2COOCH_3, II rot.), 4.55 (s, 2 H, NCH_2CO, II rot.), 4.73 (s, 2 H, NCH_2CO, II rot.), 7.26 (s, 1 H, CH=, II rot.), 7.31 (s, 1 H, CH=, I rot.), 8.02 (s, 1 H, NCHO, II rot.), 8.15 (s, 1 H, NCHO, rot). ^{13}C NMR (75 MHz, CD_3OD, I + II rot.): δ = 12.2, 36.6, 37.0, 52.8, 53.20, 143.6, 143.8, 153.0, 163.4, 164.3, 164.8, 167.0, 167.5, 169.9, 170.3, 171.4, 171.5, 171.6. MS (FAB$^+$): *m/z* = 349 [M + Na$^+$]. IR (nujol): 1852–1720 cm^{-1}.

(17) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472.

(18) The reaction has not yet been optimized. Compound **6**: mp 178–180 °C (pentane). Anal. Calcd for $C_{13}H_{16}N_4O_5$ (308.3): C, 50.48; H, 5.54; N, 18.11. Found: C, 50.40; H, 5.53; N, 18.13. ^{1}H NMR (300 MHz, $CDCl_3$), rotamers I/II, 60:40: δ = 1.93 (s, 3 H, CH_3), 3.48–3.79 (m, 4 H, NCH_2CH_2), 3.84 (s, 3 H, OCH_3), 4.14 (s, 2 H, $CH_2CO_2CH_3$, I rot.), 4.33 (s, 2 H, $CH_2CO_2CH_3$, II rot.), 4.45 (s, 2 H, NCH_2CO, I rot.), 4.66 (s, 2 H, NCH_2CO, II rot.), 6.99 (s, 1 H, CH=, I rot.), 7.04, (s, 1 H, CH=, II rot.). ^{13}C NMR (75 MHz, DMSO, I + II rot.): δ = 12.1, 12.4, 46.5, 47.8, 47.9, 48.2, 58.8, 51.9, 52.4, 108.4, 142.0, 142.1, 151.0, 164.4, 167.8, 168.4, 169.4, 169.9. MS (EI): *m/z* = 308 (M$^+$). IR (nujol): 1650–1744 (CO), 2153 (NC) cm^{-1}.

(19) An equimolar mixture of imine **11** (0.3 mmol.), 1-carboxy methylthymine **2** and isonitrile **6** in dry MeOH (1 mL) was heated under nitrogen at 60 °C for 5 min, and then stirred at r.t. for 2 d. After evaporation of the solvent, the crude mixture was purified by column chromatography (eluent: EtOAc:MeOH, 9:1, R_f = 0.31). Compound **12**: 51% yield white solid, mp 158–160 °C (pentane). Anal. Calcd for $C_{37}H_{42}N_8O_{11}$: C, 57.36; H, 5.46; N, 14.46. Found: C, 57.40; H, 5.45; N, 14.50. ^{1}H NMR (300 MHz, $CDCl_3$), rotamers I/II, 60:40: δ = 1.73–1.87 (m, 6 H, CH_3), 2.98–3.57 (m, 8 H, NCH_2CH_2N), 3.64 (s, 3 H, OCH_3, II rot.), 3.68 (s, 3 H, OCH_3, I rot.), 3.90–4.72 (m, 6 H, $NCH_2CO_2CH_3$, NCH_2CO), 5.01–5.13 (m, 2 H, OCH_2Ph), 5.59 (s, 1 H, CH, II rot.), 5.78 (s, 1 H, CH, I rot.), 5.95 (s, 1 H, NH, I rot.), 6.01 (s, 1 H, NH, II rot.), 6.67 (s, 1 H, CH=, I rot.), 6.73 (s, 1 H, CH=, II rot.), 6.98 (s, 1 H, CH=, II rot.), 7.03 (s, 1 H, CH=, I rot.), 7.24–7.35 (m, 10 H, Ph), 9.35 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$, I + II rot.): δ = 12.2, 37.5, 40.0, 44.7, 47.9, 48.2, 48.4, 48.9, 52.5, 52.8, 64.1, 66.9, 110.2, 110.4, 128.3, 128.5, 129.2, 129.9, 133.1, 136.5, 141.2, 141.7, 151.2, 151.4, 151.5, 156.7, 164.4, 164.5, 167.9, 168.3, 170.7. MS (HRMS, ESI): calcd. for $C_{37}H_{42}N_8O_{11}$: 774.2973; found: 775.3173 [M + H$^+$], 797.2903 [M + Na$^+$]. IR (nujol): 1675, b (CO) cm^{-1}.

(20) **General Procedure for the Synthesis of 13a–d:** An equimolar mixture of imines **1a–d** (0.3 mmol.), 1-carboxy methylthymine **2** and isonitrile **6** in dry MeOH (1 mL) was heated under nitrogen at 45 °C for 24 h. After evaporation of the solvent, the crude mixture was purified by column chromatography. Compound **13a**: 68% yield (eluent: EtOAc:MeOH, 95:5, R_f = 0.42), yellow-green solid, mp 176–179 °C (pentane). Anal. Calcd for $C_{40}H_{42}CrN_8O_{14}$: C, 52.75; H, 4.65; N, 12.30. Found: C, 52.70; H, 4.61; N, 12.32. ^{13}C NMR, (125 MHz, CD_3OD), I+II rot.: δ = 12.3, 12.4, 12.6, 12.7, 14.0, 38.4, 38.7, 40.8, 43.2, 44.8, 45.9, 49.9, 49.7, 64.4, 65.2, 67.6, 67.9, 91.1, 91.4, 97.9, 98.2, 98.4, 99.7, 110.6, 110.8, 129.1, 129.5, 130.2, 131.3, 135.3, 138.2, 143.6, 143.8, 144.0, 151.4, 153.1, 166.9, 169.3, 169.9, 170.3, 171.4, 172.0, 233.9. MS (ESI, HOAc): 1032.3 [M + 2 H + +2 HOAc], 933.2 [M + Na]$^+$. IR (nujol): 1966, 1886, 1664 cm^{-1}. Compound **13b**: yellow solid (30%), dr 1:1, (eluent: EtOAc:MeOH, 9:1, R_f: diast. I = 0.62, diast. II = 0.55). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 36.9, 39.0, 39.5, 44.2, 46.9, 47.0,47.2, 51.3, 54.7, 58.6, 66.1, 109.1, 109.3, 110.9, 118.6, 120.5, 121.6, 127.5, 127.9, 130.5, 135.6, 142.4, 142.6, 151.7, 162.0, 165.6, 168.4, 171.6, 232.8. Anal. Calcd for $C_{41}H_{44}CrN_8O_{15}$: C, 52.34; H, 4.71; N, 11.91. Found: C, 52.32; H, 4.70; N, 11.90. ESI-MS: 962.9 [M + Na]$^+$. IR (nujol): 1974, 1883, 1681 cm^{-1}. Compound **13c**: 53% yield, dr 1:1 (eluent: EtOAc + 5% of MeOH, Rf: diast. I = 0.44, diast. II = 0.38). Anal. Calcd for $C_{41}H_{44}CrN_8O_{14}$: C, 53.75; H, 4.80; N, 12.12. Found: C, 53.68; H, 4.81; N, 12.10. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.9, 13.5, 18.7, 28.4, 34.8, 37.19, 37.4, 38.1, 39.8, 40.2, 41.6, 41.8, 43.2, 43.4, 43.6, 43.8, 47.5, 47.8, 48.1, 48.3, 48.6, 48.8, 49.1,49.3, 49.4, 49.6, 49.7, 49.9, 50.0, 50.3, 50.6, 52.3, 52.7, 59.0, 66.6, 66.9, 86.2, 90.8, 91.6, 95.8, 96.6, 97.4, 109.9, 110.2, 110.5, 110.6, 126.5, 127.9, 128.0, 128.3, 128.5, 128.8, 129.5, 130.8, 131.1, 136.2, 138.6, 140.7, 140.9, 141.3, 150.8, 151.3, 156.4, 164.3, 167.7, 168.1, 168.3, 168.6, 170.6, 171.1, 231.4, 231.7, 232.8. MS (HRMS, ESI): calcd for $C_{41}H_{44}CrN_8O_{14}$: 924.2382; found: 947.2297 [M + Na$^+$]. IR (nujol): 1965, 1885, 1664 cm^{-1}. Compound **13d**: green solid, 28% yield, dr 1:1 (eluent: EtOAc:MeOH, 8/2 R_f: diast. I = 0.43, diast. II = 0.37). Anal. Calcd for $C_{40}H_{41}ClCrN_8O_{14}$: C, 50.83; H, 4.37; N, 11.85. Found: C, 50.78; H, 4.35; N, 11.85. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.9, 13.5, 38.1, 39.7, 40.2, 41.8, 43.4, 43.7, 48.2, 52.7, 54.7, 66.6, 66.8, 90.9, 91.7, 95.8, 96.7, 97.4, 110.5, 110.7, 126.5-129.5, 140.3, 140.9, 150.7, 151.1, 151.3, 164.3, 164.5, 167.5, 168.2, 168.4, 172.0, 231.7, 231.9. ESI-MS: *m/z* = 967.1 [M + Na]$^+$. IR (nujol): 1977, 1938, 1912, 1682 cm^{-1}.

(21) **General Procedure for the Ester Hydrolysis in Compounds 13a–d:** LiOH (0.11 mmol, 5 equiv) was added to a solution of **13a–d** (1 equiv) in MeOH (3 mL) and the mixture stirred for 6 h at r.t. (TLC, eluent: EtOAc:MeOH, 8:2, R_f = 0.1). H_2O (5 mL) was added and the solution treated with $KHSO_4$ (0.8 mL of 1 M solution). After extraction with EtOAc (3 × 10 mL) the crude solid product was suspended in pentane and filtered. Selected data for **14a–d**. Compound

14a: light-green solid, mp 205 °C (dec.). Anal. Calcd for $C_{39}H_{40}CrN_8O_{14}$: C, 52.23; H, 4.50; N, 12.50. Found: C, 52.12; H, 4.48; N, 12.51. ESI-MS: *m/z* = 895.2 $[M - H]^-$. IR (nujol): 1966, 1891, 1669 cm^{-1}. Compound **14b**: light-green solid. Anal. Calcd for $C_{40}H_{42}CrN_8O_{15}$: C, 51.84; H, 4.57; N, 12.09. Found: C, 51.82; H, 4.58; N, 12.10. ESI-MS: *m/z* = 925.1 $[M - H]^-$. IR (nujol): 1964, 1881, 1686 cm^{-1}. Compound **14c**: light-green solid. Anal. Calcd for $C_{40}H_{42}CrN_8O_{14}$: C, 52.75; H, 4.65; N, 12.30. Found: C, 52.13; H, 4.67; N, 12.31. ^{13}C NMR (75 MHz, DMSO): 11.7, 12.1, 13.4, 18.0, 18.5, 21.0, 28.8, 26.2, 36.2, 37.0, 37.4, 42.7, 43.5, 46.1, 46.6, 47.8, 48.6, 49.2, 65.4, 65.6, 89.6, 93.4, 97.5, 107.7, 108.0, 112.8, 126.2, 127.7, 128.2, 137.0, 142.1, 142.3, 148.9, 150.9, 156.0, 161.7, 164.3, 166.9, 167.3, 167.6, 168.1, 172.0, 233.7, 233.2. ESI-MS: *m/z* = 909.2 $[M - H]^-$, 933.4 $[M + Na]^+$. IR (nujol): 1966, 1889, 1669 cm^{-1}. Compound **14d**: light-green solid. Anal. Calcd for $C_{39}H_{39}ClCrN_8O_{14}$: C, 50.30; H, 4.22;N, 12.03. Found: C, 50.20; H, 4.20; N, 12.00. ESI-MS: *m/z* = 928.9 $[M - H]^-$. IR (nujol): 1977, 1912, 1680 cm^{-1}.