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SYNTHESES OF SUBUNITS OF CALICHEMICINS γ_1^I

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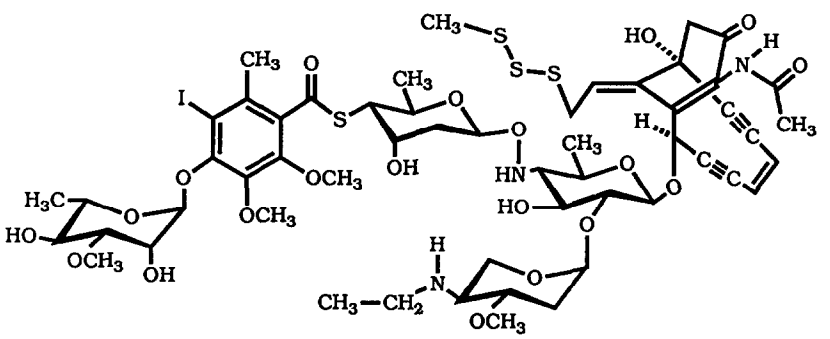
Abstract - The first syntheses of calichemicin subunits **6** and **12** are described. They are useful building blocks for the synthesis of the oligosaccharide moiety of **1**.

The calichemicins[1] represent a new class of compounds known to be active against various solid tumors and leucemia in mice.[2] Lee et al.[1] isolated the calichemicins from a fermentation broth of *micromonospora echinospora* ssp. calichensis. They investigated their biological activity and elucidated the structure of calichemicin γ_1^I **1**. The activity of the calichemicins is based on a sequence specific cleavage of double-stranded DNA. The oligosaccharide moiety including the highly substituted aromatic carboxylic acid is responsible for the sequence selectivity observed, while the aglycon with its enediyne-structure is causes the strand cleavage.[3-5]



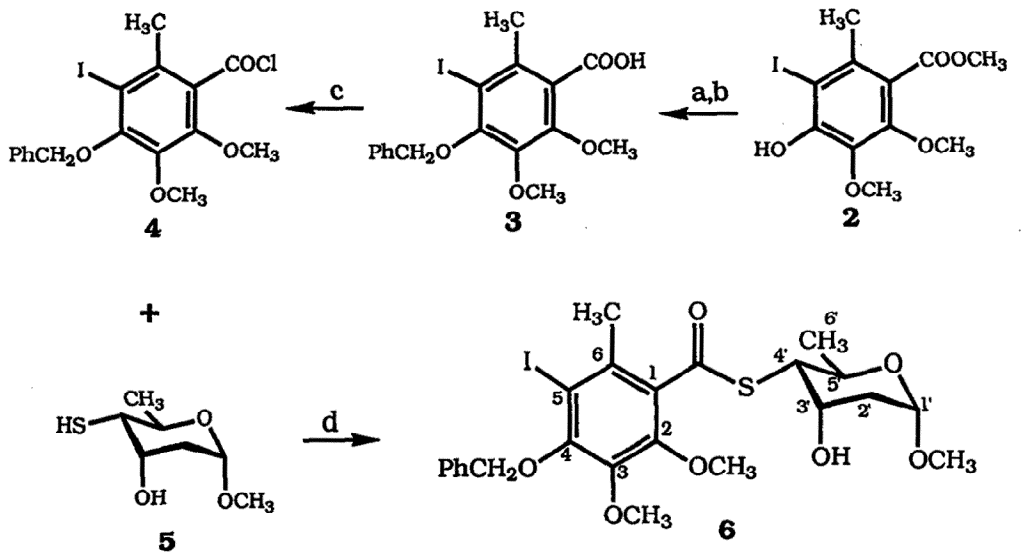
1

The importance of the saccharide part for the biological activity motivated us to synthesize subunits of the calichemicins. We now describe the first syntheses of the fragments **6** and **12**.

The synthesis of the thiobenzoate subunit **6** starts from the aromatic compound **2**[6] and the thiosugar **5** we described recently.[7,8] For the preparation of **4** the phenolic hydroxyl group in **2** is protected as its benzyl ether (92%). The ester is then hydrolysed to yield the acid **3** (81%). The conversion to the desired acyl chloride **4** is achieved with 1-chloro-N,N,2-trimethylpropenylamine[9] (95%). The reaction of the thiosugar **5** with the acyl chloride **4** in pyridine leads to the product **6** as a crystalline solid (59%).

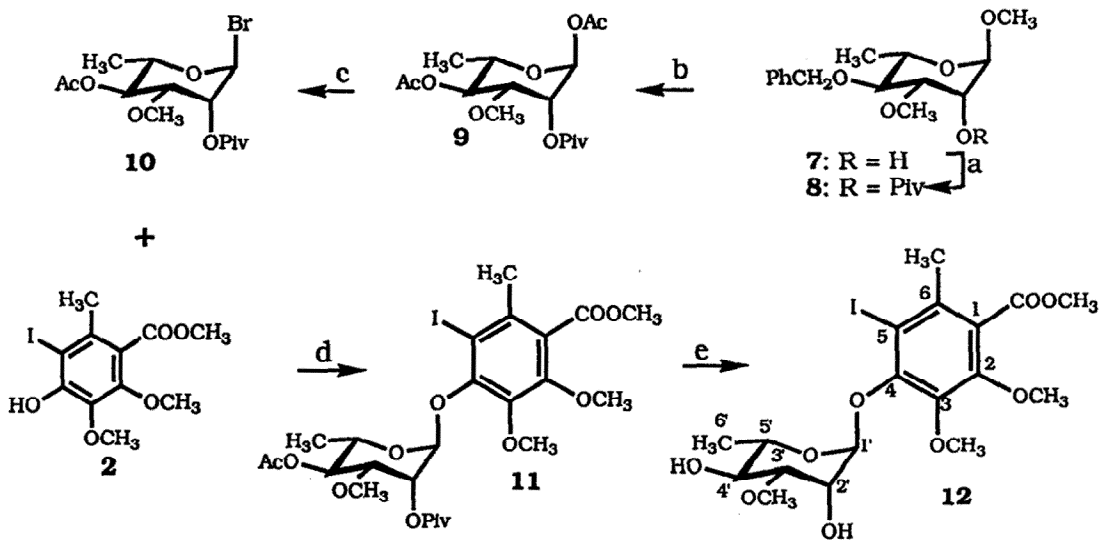
For the synthesis of the subunit **12** the glycosyl bromide **10** - suitable for the glycosidic coupling with **2** - had to be prepared. Therefore **7**[10] is treated with pivaloyl chloride to yield **8** (95%). The pivaloyl residue guarantees the 1,2-trans-glycosidic coupling. Furthermore the pivaloyl residue is suitable to diminish byproducts in the glycosylation step.[11]

Synthesis of 6



a) 1.1 equiv. $PhCH_2Br$, K_2CO_3, acetone, 2h reflux (92%). b) 3 equiv. 5n-NaOH, DMSO, 3h, 100°C (81%). c) 1.2 equiv. 1-chloro-N,N,2-trimethylpropenylamine, dichloromethane, 3h, 0°C → 25°C (95%). d) 1.5 equiv. **4**, pyridine, 2d, 0°C → 25°C (59%).

Synthesis of 12



a) PivCl, pyridine, 18h, 25°C (96%). b) AcOH, Ac_2O, H_2SO_4 (32/32/1, v/v/v), 16h, 25°C (98%). c) HBr/AcOH, dichloromethane, 18h, 0°C → 25°C (94%). d) Ag_2CO_3 on Celite, toluene, 4h, 50°C (41%). e) CH_3ONa, CH_3OH, 3d, 25°C (52%).

The following acetolysis gives **9** under simultaneous substitution of the benzyl ether by an acetyl group. The conversion of **9** to the glycosyl bromide **10** is accomplished with hydrogen bromide in acetic acid (93%). The α-glycosidic coupling of **10** and **2** leading to the product **11** is achieved with silver carbonate on Celite as catalyst.[12] Cleavage of the ester groups in the 2- and 4-position of the carbohydrate residue leads to the subunit **12** as a colourless crystalline solid.

Synthetically produced structures are easily modified in their chemical structure. Therefore they are suitable subjects for the investigation of their interaction with DNA and of transport phenomena. Furthermore the compounds **6** and **12** are useful building blocks for the synthesis of the oligosaccharide part of the calichemicins, which is now in progress in our laboratory.

Physical and spectroscopic data of the compounds*

^{1}H NMR spectra: 300 MHz, $CDCl_3$, 25°C, TMS, ^{13}C NMR spectra: 75MHz, $CDCl_3$, 25°C, TMS, if not otherwise noted.

3: colourless solid, m.p. = 140°C.

4: sirup, ^{1}H NMR: δ = 2.45 (s, 3H, CH_3-Ar), 3.88, 4.00 (2s, 2x3H, 2xOCH_3), 5.07 (s, 2H, $\underline{CH_2}$Ph), 7.3-7.7 (m, 5H, $CH_2\underline{Ph}$). - ^{13}C NMR : δ = 25.34 (CH_3-Ar), 61.18, 61.69 (2xOCH_3), 75.17 ($\underline{CH_2}$Ph), 94.49 (C-5), 128.40, 128.46, 128.64 (o, m, p-Ph), 129.70 (C-1), 132.09, 136.37 (C-3, -6), 143.75 (C-1'-Ph), 149.68, 154.40 (C-2, -4), 167.25 (COCl). IR: 1788 cm^{-1} (C=O).

6: colourless solid, m.p. = 153°C. $[\alpha]_D^{25} = +93.5°$ (c = 0.85, $CHCl_3$). - ^{1}H NMR : (300MHz, C_5D_5N, 25°C, TMS) δ = 1.61 (d, $^3J_{5,6}$ = 6.4 Hz, 3H, CH_3-6'), 2.09 (dt, $^2J_{2ax,2eq}$ = 14.3 Hz, $^3J_{1,2ax}$ = 3.5 Hz, 1H, H-2'ax), 2.19 (ddd, $^3J_{2,3}$ = 3Hz, $^3J_{1,2eq}$ = 1.3 Hz, 1H, H-2'eq), 2.52 (s, 3H, CH_3-Ar), 3.33 (s, 3H, OCH_3-1'), 3.82, 4.02 (2s, 2x3H, 2xOCH_3-Ar), 4.24 (dd, $^3J_{4,5}$ = 10.7 Hz, $^3J_{3,4}$ = 2.7 Hz, 1H, H-4'), 4.37 (bs, 1H, H-3'), 4.48 (dq, 1H, H-5'), 4.89 (d, 1H, H-1'), 5.12 (s, 2H, $\underline{CH_2}$Ph), 5.48 (broad, 1H,OH), 7.2-7.8 (m, 5H, $CH_2\underline{Ph}$). - ^{13}C NMR (75MHz, C_5D_5N, 25°C, TMS): δ = 19.11 (C-6'), 25.17 ($\underline{C}H_3$-Ar), 37.12 (C-2'), 52.50 (C-4'), 55.06 (OCH_3-1'), 61.07, 61.98 (2xOCH_3-Ar), 63.77, 67.56 (C-3', -5'), 75.22 ($\underline{CH_2}$Ph), 95.79 (C-5'), 98.76 (C-1'), 128.58, 128.79, 128.98 (o,m,p-$\underline{Ph}$), 131.57 (C-1), 133.26, 137.44 (C-3, -6), 144.44 (C-1-Ph), 150.94, 154.01 (C-2, C-4), 193.15 ($\underline{C}OS$).

8: sirup, $[\alpha]_D^{25} = -41.7°$ (c = 0.73, $CHCl_3$).

9: colourless solid, m.p. = 89°C. $[\alpha]_D^{25} = -26.3°$ (c = 1.32, $CHCl_3$). - ^{1}H NMR : d = 1.20 (d, $^3J_{5,6}$ = 6.4 Hz, 3H, H-6), 1.25 (s, 9H, Piv), 2.08, 2.13 (2s, 2x3H, Ac-C-1, -4), 3.33 (s, 3H, OCH_3), 3.60 (dd, $^3J_{3,2}$ = 3.4 Hz, $^3J_{3,4}$ = 9.7 Hz, 1H, H-3), 3.84 (qd, $^3J_{4,5}$ = 9.7 Hz, 1H, H-5), 5.00 (d, 1H, H-4), 5.30 (dd, $^3J_{1,2}$ = 2.0 Hz, 1H, H-2), 6.01 (d, 1H, H-1). - ^{13}C NMR: δ = 17.62 (C-6), 20.87, 20.92 (Ac-C-1,-4), 27.09 (CH_3-Piv), 39.02 (C_q-Piv), 57.51 (CH_3, C-3), 66.25, 68.78, 72.04, 77.01 (C-2,-3,-4, -5), 91.09 (C-1), 168.39, 169.83 (C=O, Ac), 177.30 (C=O, Piv).

10: sirup. ^{1}H NMR : δ = 1.25 (d, $^3J_{5,6}$ = 6.4 Hz, 3H, H-6), 1.25 (s, 9H, Piv), 2.11 (s, 3H, Ac), 3.33 (s, 3H, OCH_3), 4.00 (qd, $^3J_{4,5}$ = 9.8 Hz, 1H, H-5), 4.10 (dd, $^3J_{3,4}$ = 9.8 Hz, $^3J_{2,3}$ = 3.0 Hz, 1H, H-3), 5.05 (t, 1H, H-4), 5.50 (dd, $^3J_{1,2}$ = 1.7 Hz,

1H, H-2), 6.30 (s, 1H, H-1).

11: sirup, $[\alpha]_D^{25} = -20.1°$ (c = 1.12, $CHCl_3$).

12: colourless solid, m.p. = 143°C. $[\alpha]_D^{25} = -37.5°$ (c = 0.72, $CHCl_3$). ^{1}H NMR: δ = 1.31 (d, $^3J_{5,6}$ = 6.2 Hz, 3H, CH_3-6'), 2.37 (s, 3H, CH_3-Ar), 3.57 (s, 3H, OCH_3-C-3'), 3.65 (t, $^3J_{3,4}$ = 9.4 Hz, $^3J_{4,5}$ = 9.4 Hz, 1H, H-4'), 3.87 (dd, $^3J_{2,3}$ = 3.2 Hz, 1H, H-3'). 3.85, 3.88, 3.92 (3s, 3x3H, $COOCH_3$, 2xOCH_3-Ar), 4.20 (dq, 1H, H-5'), 4.48 (dd, $^3J_{1,2}$ = 1.6 Hz, 1H, H-2'), 5.75 (d, 1H, H-1'). - ^{13}C NMR: δ = 17.58 (C-6'), 25.94 (CH_3-Ar), 52.53 ($COO\underline{C}H_3$), 57.19 ($O\underline{C}H_3$-C-1'), 60.90, 61.53 (2x$O\underline{C}H_3$-Ar), 67.04, 70.39, 71.19, 80.91 (C-2', -3', -4', -5'), 93.19 (C-5), 102.48 (C-1'), 125.47 (C-1), 134.18, 142.97 (C-2, -4), 151.00, 151.25 (C-3, -5), 167.64 ($\underline{C}OOCH_3$).

* NMR data of all compounds described can be requested from the authors.

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References

1. M.D. Lee, T.S. Dunne, M.M. Siegel, C.C. Chang, G.O. Morton, D.B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3464; M.D. Lee, T.S. Dunne, C.C. Chang, G.A. Ellestad, M.M. Siegel, G.O. Morton, W.J. McGahren, D.B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3466.
2. J.P. Thomas, S.G. Carvajal, H.L. Lindsay, R.V. Citarella, R.E. Wallace, M.D. Lee, F.E. Durr, 26th Interscience Conference on Antimicrobial agents and Chemotherapie, New Orleans, LA, Sept. 1986, American Society for Microbiologie, Washington DC, Program and Abstracts; Abstract 229.
3. N. Zein, A.M. Sinha, W.J. McGahren, G.A. Ellestad, *Science* **1988**, *240*, 1198.
4. R.C. Hawley, L.L. Kiessling, S.L. Schreiber, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 1105.
5. N. Zein, M. Poncin, R. Nilakantan, G.A. Ellestad, *Science* **1989**, *244*, 697.
6. The first synthesis of **2** was described by Nicolaou et.al.: K.C. Nicolaou, T. Ebata, N.A. Stylianides, R.D. Groneberg, P.J. Carrol, *Angew. Chem.* **1988**, *100*, 1138; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1097.
7. K. van Laak, H.-D. Scharf, *Tetrahedron* **1989**, *45*, 5511.
8. K. van Laak, H.-D. Scharf, *Tetrahedron Lett.* **1989**, *30*, 4505.
9. A. Devos, J. Remion, A.-M. Frisque-Hesbain, A. Colens, L. Ghosez, *J. Chem. Soc. Chem. Commun.* **1979**, 1180.
10. V. Pozsgay, P. Nánási, *Carbohydr. Res.* **1980**, *81*, 184.
11. H. Kunz, A. Harreus, *Liebigs Ann. Chem.* **1982**, 41.
12. J. Hartenstein, G. Satzinger, *Liebigs Ann. Chem.* **1974**, 1763.

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