An unprecedented octahydro-3 H-oxeto[2,3,4-ij]isochromene ring system formed by a trichloromethyl-anion-induced reaction cascade

Wital Schmidt^a
 Peter G. Jones^b
 Jennifer Herrmann^c
 Rolf Müller^c
 Stefan Schulz^{*a}

^a Institute of Organic Chemistry, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany.

^b Institute of Inorganic and Analytical Chemistry, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany.

^c Department Microbial Natural Products, Helmholtz Institute for Pharmaceutical Research Saarland, Helmholtz Centre for Infection Research, Saarland University, Campus E8.1, 66123 Saarbrücken, Germany.

* indicates the main/corresponding author.

stefan.schulz@tu-bs.de

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Abstract Sigillin A is a unique polychlorinated, insect repellent natural product, isolated recently from springtails. During the exploitation of an access to such compounds using a trichloromethyl-anion-induced epoxide opening as key step a new synthetic compound was found. A five-step cascades reaction leads to an oxeto[2,3,4-ij]isochromene compound, including a rare oxetane acetal as well as an trichloroether group. Biological data on the antibacterial properties of this compound and sigillin A are reported as well.

Key words Sigillin, Springtails, dichlorocarbene, chlorinated natural products, hydrobenzopyranone, dimethyldioxirane, oxetane acetal, trichloroether

The polychlorinated hydrobenzopyranone derivative sigillin A (1) and its congeners were recently isolated from the winter-active springtail *Ceratophysella sigillata*, which lives in Central Europe.¹ They form a unique class of natural products with

insect-repellent activity. *C. sigillata*, also called the snow flea because of its striking winter activity period, uses sigillin A as a chemical defense against various arthropod predators.²

During our work on the sigillin compound family we became interested in the synthesis of sigillin derivatives to evaluate the biological activity of this remarkable class of compounds. Our initial targets were didesoxysigillins such as 3 that lacked one hydroxy and one acetoxy group. While we successfully synthesized 3, the otherwise straightforward synthesis was hampered by the last step, a ketone dichloromethylenation, which gave poor yields.¹ Sigillin F (2) is the second most abundant natural sigillin. Access to its dideoxy analogue 4 might be possible by opening of epoxide 5 with a trichloromethyl anion (Scheme 1), and the epoxide should in turn be accessible via epoxidation of the known alkene 6.¹ We hoped that compound 3 could be developed by elimination of HCl from 4, thus avoiding dichloromethylenation.

Scheme 1 Sigillins A (1) and F (2) and a retrosynthetic approach to their synthesis.

Therefore, lactone 6 was epoxidized with mCPBA, but only a moderate yield of 54% of a diastereomeric mixture of epoxides

8 and 9 was obtained, accompanied by ring-opened products formed by addition of m-chlorobenzoic acid (Scheme 2). Better

results were obtained with dimethyldioxirane (DMDO),³ resulting in an almost quantitative conversion leading to a 1:2 mixture of the two epoxides **8** and the major compound **9**, separable by column chromatography. Because the

trichloromethyl group tends to promote crystallization, X-ray crystallography allowed the assignment of the diastereomers (see SI).

Scheme 2 Synthesis of epoxides **8** and **9** and reaction with trichloromethyl lithium.

Various methods were used for generation of the trichloromethyl anion. Trimethyl(trichloromethyl)silane and LiHMDS⁴ proved to be insufficiently reactive, leading to unreacted starting material and minor amounts of side products. The reaction of trichloromethyl lithium, generated from chloroform and *n*-butyl lithium, in the presence of boron trifluoride etherate⁵ at -95°C furnished the lactone-opened product **12**, because the Lewis acid activated the ester group, but not the epoxide. Omission of the Lewis acid reduced activity, leading to no observable reaction. To increase reactivity, a large excess of the anion was used, accompanied by an increase of the reaction temperature to -60°C after anion generation. Epoxide-opened products were indeed observed, but the outcome was unexpected. Epoxide **9** was converted not into the desired product **4**, but the chloride **11**. Obviously, the relatively small chloride ion reacted instead of the trichloromethyl anion, for which axial attack is hindered by the quasi-axial bridgehead methyl group. Chloride attack occurred regioselectively on epoxide carbon **1a** in agreement with the Fürst-Plattner rule,⁶ leading to a *trans*-diaxial halohydrine structure (Scheme 3).

Scheme 3 Regioselectivity of the nucleophilic attack on the epoxides **8** and **9**.

In the case of diastereomer **8**, axial attack of the epoxide seems to be hindered by the ester and bulky trichloromethyl-groups. Instead of the desired product, the unexpected tricyclic compound **10** was formed.⁷ The structure, exhibiting an unusual oxetane, as part of an acetal, and nine chlorine atoms, was confirmed by X-ray crystallography (Figure 1).⁸

Figure 1 ORTEP diagram of X-ray analysis of octahydro-3H-oxeto[2,3,4-ij]isochromene (**10**).

The formation of **10** can be explained by the involvement of both the trichloromethyl-anion and dichlorocarbene in the reaction (Scheme 4). Above -70°C , the trichloromethyl-anion exists in equilibrium with dichlorocarbene and Cl^- .⁹ In a cascade reaction the trichloromethyl-anion first attacks the carbonyl group of **8**, bringing the oxygen-anion thus formed into close proximity with the epoxide. The epoxide is now opened, and the resulting alkoxy-anion **14** can react with dichlorocarbene. The new anion **15** cannot stabilize itself and reacts with a second dichlorocarbene to form the third anion **16**, which loses chloride to form **10**. A five step sequence is followed to arrive at the final product. Alternatively, a substitution of the alkoxide **14** at tetrachloroethene might also be possible, although not very probable because of the low concentration of this dichlorocarbene dimerization product in the reaction mixture. The presence of dichlorocarbene was also supported by small amounts of 2-dichloromethyltetrahydrofuran, tetrachloroethene, and 1,1-dichloro-2,3-dipropylcyclopropane in the reaction mixture, as detected by GC/MS.

According to the Fürst-Plattner rule,⁶ the epoxide is now regioselectively opened at C-7b (Scheme 3). Direct attack of a nucleophile, e. g. Cl^- or CCl_3^- on the epoxide is hindered by the adjacent carbonyl group. Therefore, the nucleophile in this case attacks the carbonyl group from the least hindered side. Now the oxy-anion in **13** is properly positioned to attack C-7b, leading to the observed stereo- and regioselectivity of the reaction cascade.

Scheme 4 Proposed mechanism for the formation of **10**.

Acetal **10** is stable and can be isolated by column chromatography. Obviously the large chlorine substituents shield the compound from attack and the acetal group itself is stabilized by the strongly electron-withdrawing trichloromethyl-groups. The almost planar oxetane ring and the trichloromethyl-substituents lead to a boat-like conformation of the two six-membered rings (Figure 1).

The tricyclic 3H-oxeto[2,3,4-ij]isochromene ring system has not been reported before. Even the simpler 2,8-dioxabicyclo[4.2.0]octane system has only rarely been prepared, using photochemistry¹⁰ and cycloadditions.¹¹ A nucleophilic displacement to form this type of acetal has not been reported before, to the best of our knowledge.

Sigillin A (**1**) is highly active as an insect-repellent.¹ We were also interested whether **1** or the new compound **10** had other biological activities. Therefore, they were tested for antimicrobial and cytotoxic activity. Whereas no antimicrobial activity was observed, both compounds showed some cell toxicity, for **10** in the low μM range (see SI). Although no antibacterial was observed until a concentration of $2\ \mu\text{M}$ with human pathogenic bacteria, it might be possible that **1** indeed protects the springtails against microorganisms, because its concentration in the springtail can reach $4\ \text{mM}$.¹

In summary, although the original synthetic idea leading to sigillins was unsuccessful, a unique cascade reaction has been discovered, leading to a new, highly chlorinated tricyclic system.

Acknowledgment

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Supporting Information

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Primary Data

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References and Notes

- (1) Schmidt, W.; Schulze, T. M.; Brasse, G.; Nagrodzka, E.; Maczka, M.; Zettel, J.; Jones, P. G.; Grunenberg, J.; Hilker, M.; Trauer-Kizilelma, U. et al., *Angew. Chem. Int. Ed.* 2015, 54, 7698–7702.
- (2) Zettel, J.; Zettel, U., *Mitt. Naturforsch. Ges. Bern* 2008, 65, 79–110.
- (3) Crandall, J. K.; Rambo, E., *Tetrahedron* 2002, 58, 7027–7036.
- (4) Henegar, K. E.; Lira, R., *J. Org. Chem.* 2012, 77, 2999–3004.
- (5) Imai, T.; Nishida, S.; Tsuji, T., *J. Chem. Soc., Chem. Commun.* 1994, 2353–2354.
- (6) Fürst, A.; Plattner, P. A., *Helv. Chim. Acta* 1949, 32, 275–283.
- (7) Synthesis of 10: Abs. CHCl_3 (0.478 g, 0.323 mL, 4.00 mmol) was added to abs. THF (15 mL), cooled to -98°C and finally nBuLi (2.50 mL, 1.6M in hexane, 4.00 mmol) was added. After stirring for 15 min, a solution of epoxide 8 (24 mg, 0.08 mmol) in abs. THF (1 mL) was slowly added. The reaction mixture was allowed to warm up to -60°C during 3 h. After hydrolysis with sat. aq. NH_4Cl , the phases were separated and the water phase extracted three times with dichloromethane. The combined organic phases were dried with MgSO_4 , filtered, and the solvent was evaporated. The crude product was purified by flash chromatography on silica (pentane/diethyl ether 10:1). The product was isolated as colorless crystals (13 mg, 0.024 mmol, 30 %). $R_f = 0.61$ (Pentane/ Et_2O 2:1) ^1H -NMR (400 MHz, CDCl_3 , TMS): δ [ppm] = 5.00 (d, 1H, H-7a, $^3J_{\text{H,H}} = 3.8$ Hz), 4.95 (dd, 1H, H-3, $^3J_{\text{H,H}} = 8.5$ Hz, $^3J_{\text{H,H}} = 7.2$ Hz), 4.76 (ddd, 1H, H-7, $^3J_{\text{H,H}} = 12.8$ Hz, $^3J_{\text{H,H}} = 4.4$ Hz, $^3J_{\text{H,H}} = 3.8$ Hz), 2.68 (dddd, 1H, H-4a, $^3J_{\text{H,H}} = 13.4$ Hz, $^3J_{\text{H,H}} = 11.1$ Hz, $^3J_{\text{H,H}} = 7.8$ Hz, $^3J_{\text{H,H}} = 5.8$ Hz), 2.17 – 2.08 (m, 1H, H-6), 2.14 – 2.06 (m, 1H, H-4), 2.07 – 1.99 (m, 1H, H-5), 1.83 (ddd, 1H, H-4, $^2J_{\text{H,H}} = 13.6$ Hz, $^3J_{\text{H,H}} = 13.0$ Hz, $^3J_{\text{H,H}} = 8.6$ Hz), 1.71 – 1.64 (m, 1H, H-5), 1.69 – 1.60 (m, 1H, H-6), 1.46 (s, 3H, CH_3). ^{13}C -NMR (100 MHz, CDCl_3 , TMS): δ [ppm] = 139.99 (COCl), 109.36 (CCl_2), 108.71 (C-1a), 100.44 (1a- CCl_3), 99.78 (3- CCl_3), 86.47 (C-7a), 84.35 (C-3), 82.14 (C-7), 44.73 (C-1a), 33.64 (C-4a), 26.36 (C-4), 22.88 (C-6), 21.15 (C-5), 10.20 (CH_3). HR-MS (ESI $^+$): calc.: 566.7959 [M+Na] $^+$, found: 566.7960.
- (8) CCDC numbers: 8 CCDC 1504299; 9 CCDC 1504300; 10 CCDC 1504301; 11 CCDC 1504302
- (9) Köbrich, G., *Angew. Chem. Int. Ed. Engl.* 1972, 11, 473–485.
- (10) (a) Griesbeck, A. G.; Stadtmueller, S., *J. Am. Chem. Soc.* 1990, 112, 1281–1283. (b) Adam, W.; Kliem, U.; Peters, E. M.; Peters, K.; Schnering, H. G. von, *J. Prakt. Chem.* 1988, 330, 391–405.
- (11) (a) Karakhanov, E. A.; Lysenko, S. V.; Kovaleva, N. F.; Brezhnev, L. Y.; Glukhovtsev, V. G.; Karakhanov, R. A., *Vestn. Mosk. Univ., Ser. 2: Khim.* 1982, 23, 159–163. (b) Sugimura, H.; Osumi, K., *Tetrahedron Lett.* 1989, 30, 1571–1574.