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## SYNTHESIS AND BIOLOGICAL EVALUATION OF A NOVEL ACRONYCINE/DUOCARMYCIN HYBRID NATURAL PRODUCT

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**Abstract** – The design of novel natural product hybrids consisting of parts of two or more bioactive compounds may allow an access to new drugs. Here we describe the synthesis of **3**, a hybrid of the cytotoxic acronycine (**2**) and *seco*-duocarmycin (*seco*-**1**), which was prepared via a selective bromination of **7** followed by the introduction of an alkyne moiety, which was further manipulated to give the epoxide **12**. Cyclisation and chlorination of the formed primary hydroxy group yielded **3**, which in situ would give the desired hybrid **4**. The in-vitro-cytotoxicity test revealed a slightly higher bioactivity of the hybrid **3** compared to acronycine (**2**).

### INTRODUCTION

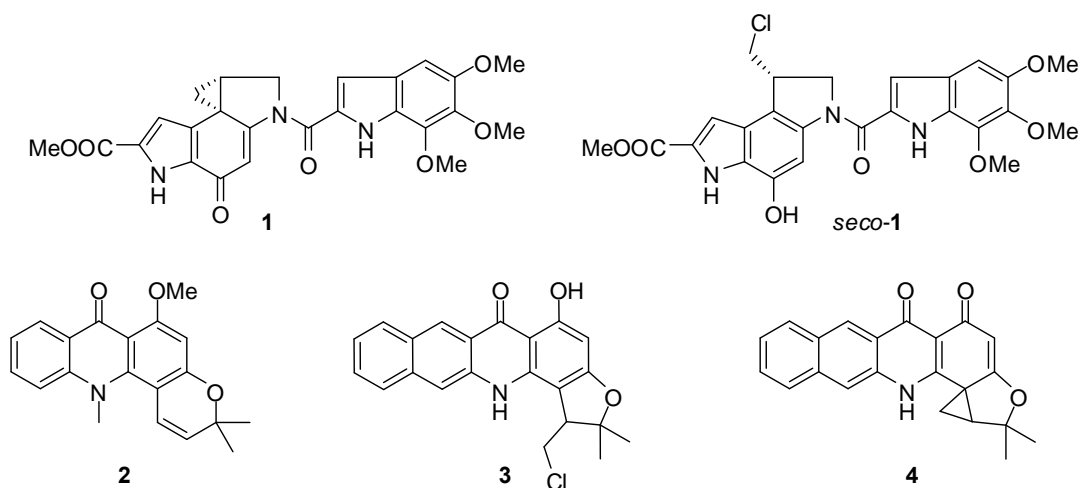
Nature is an excellent source of lead structures for the fight against any type of disease. In fact, approximately 42% of the drugs that have been approved in the last 25 years are either natural products or derivatives and analogues thereof.<sup>1</sup> For anti-cancer agents the percentage is even higher, 52% of the approved drugs are nature derived and nearly all immunosuppressive drugs needed in transplantations are natural products or their derivatives.<sup>1</sup> Although the number of natural products being huge in the end it is limited, whereas millions of hybrids as combinations of parts of different natural products can be prepared. Recently, we and others have introduced the concept of natural product hybrids and shown its usefulness. Thus, these hybrids often exceed their parent compounds in biological activity or have other useful properties.<sup>2</sup> One example for a natural hybrid is the indole alkaloid vincristine,<sup>3</sup> a well known drug in cancer chemotherapy. It is a dimeric indole alkaloid consisting of vindoline – an alkaloid of the *Aspidosperma* subgroup – and catharanthine – a member of the *Iboga* subgroup of indole alkaloids.

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Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77<sup>th</sup> birthday.

Interestingly, both monomers do not show any useful biological activity. In our approach for a selective treatment of cancer on the basis of the antibody directed enzyme prodrug therapy (ADEPT) we also used hybrids which consist of analogous of the antibiotic duocarmycin SA (**1**) and a sugar moiety (figure 1).<sup>4</sup> Here a reduction of the cytotoxicity is the goal.

In our search for new anti cancer compounds with better tolerance we here describe the preparation of a new hybrid of duocarmycin SA (**1**) in its *seco*-form with the acridone alkaloid acronycine (**2**), which was first isolated from *Acronychia baueri* Schott (Rutaceae) in 1948 (Figure 1). Acronycine (**2**) shows a broad spectrum of activity against numerous cancer models and its cytotoxicity is based on an intercalation with double stranded DNA due to its planar aromatic system which is followed by an alkylation probably via the intermediate formation of an epoxide.<sup>5</sup> However, clinical trials employing **2** and benzo[*b*]acronycine, respectively gave only poor results mainly because of their moderate potency and low water-solubility.<sup>6</sup>



**Figure 1.** Natural products duocarmycin SA (**1**) and acronycine (**2**), *seco*-duocarmycin (*seco*-**1**) and hybrid compounds **3** and **4**.

On the other hand, duocarmycin SA (**1**), isolated in 1986 from *Streptomyces* sp. DO-113, shows a very high cytotoxicity with an  $IC_{50} = 10$  pM,<sup>7</sup> but has severe side effects such as myelotoxicity.<sup>8</sup> The spirocyclopropylcyclohexadienone moiety together with the DNA-binding unit in duocarmycin SA (**1**) and similar compounds allows an irreversible intercalation into the minor groove of the DNA to induce apoptosis.<sup>4</sup>

For a combination of the positive effects of duocarmycin SA (**1**) and acronycine (**2**), we designed the novel acronycine/*seco*-duocarmycin hybrid **3**, which would be transformed *in situ* by a *Winstein* cyclisation<sup>9</sup> into the active hybrid natural product species **4**, comprising the acridone structure of acronycine (**2**) and the spirocyclopropylhexadienone moiety of duocarmycin SA (**1**).

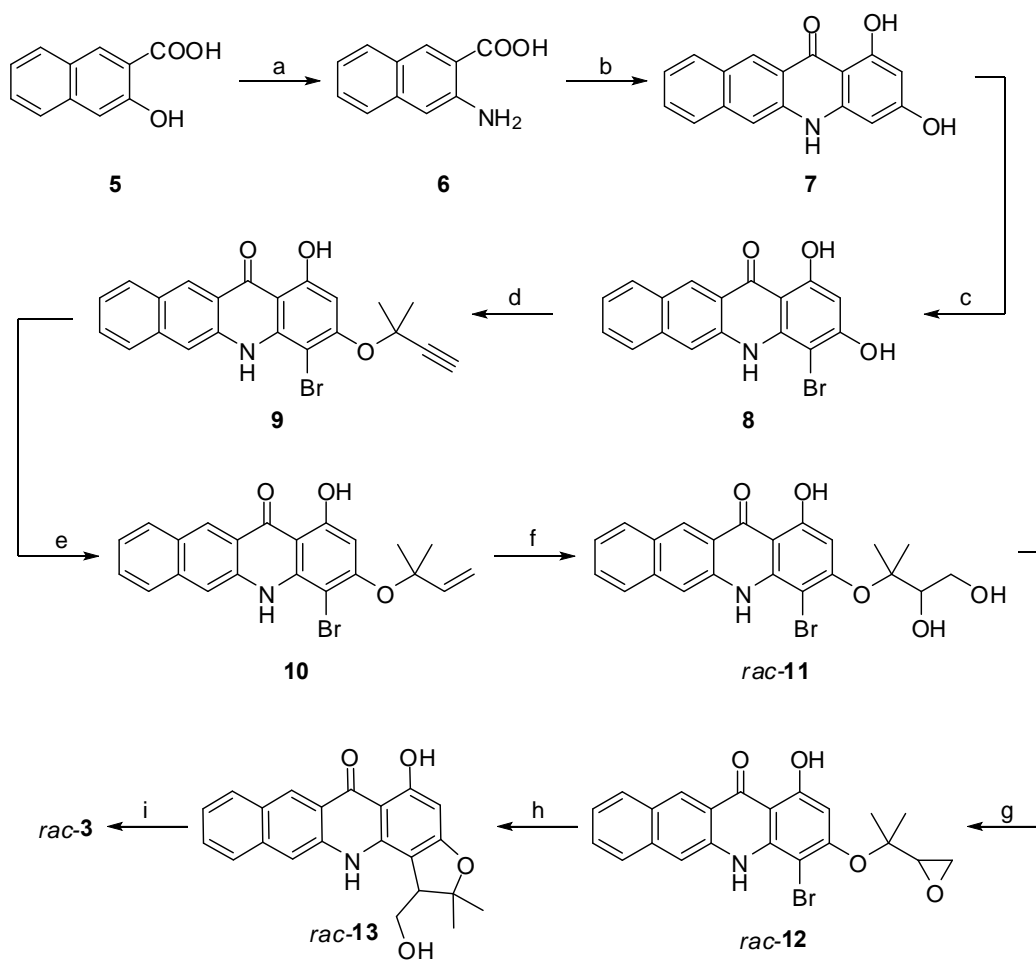
## RESULTS AND DISCUSSION

**Synthesis of a novel acronycine/duocarmycin hybrid natural product 4:** Our approach for the synthesis of **4** was based on the formation of the chloride **3** from the hydroxy compound **13**, which on the other hand should be accessible from **12** containing an aryl bromide and an epoxide moiety. Thus, halogen-metal exchange followed by a nucleophilic attack with opening of the epoxide would directly lead to **13**. However, all attempts to transfer **8** into **12** in a straight forward approach using for instance the methanesulfonate of the epoxide of 1,1-dimethylallylic alcohol were not successful, since under the reaction conditions only the corresponding propenyloxirane was formed. Therefore, we used 3-chloro-3-methylbutyne for the alkylation of **8** with further manipulations to give **12**. At this stage we did not try to develop an enantioselective synthesis, since we did not know which of the two enantiomers would be more active.

Commercially available 2-hydroxynaphthoic acid (**5**) was reacted with zinc chloride in aqueous, saturated ammonia solution at 190 °C for 4.5 d to give the amino acid **6** in 60% yield.<sup>10</sup> Fusion with phloroglucinol (1,3,5-trihydroxybenzene) using catalytic amounts of tosylic acid in *n*-heptanol under reflux for 19 h led to the acridone **7** in 59% yield.<sup>11</sup> Selective bromination at C-4 was achieved via a complexation of the vinylogous acid functionality with zinc chloride and subsequent addition of one equivalent of NBS in acetone at -78 °C for 2 h to give **8** in 59% yield. In addition, 15% of the 2-bromo derivative and 4% of the dibromo compound besides 18% of the starting material were obtained. The yield of **8** could be improved to 70% using 1.35 equivalents of NBS under otherwise identical reaction conditions with the disadvantage of the additional formation of 18% of the dibromo compound which was difficult to separate from **8**. Other complexing agents as CuCl<sub>2</sub> afforded lower yields of **8**. Interestingly, reaction of **7** with 1.00 equivalent of NBS at -78 °C without the addition of ZnCl<sub>2</sub> gave the unwanted 2-bromo compound as the main product with 43% yield. Monoalkylation with 3-chloro-3-methyl-1-butyne using catalytic amounts of copper(I) chloride in DMF at rt for 24 h yielded **9** in 68%. For this transformation the use of a Zn-salt as ZnBr<sub>2</sub> as an additive was less appropriate, since only 6% of the desired **9** was obtained, the main product with 34% was a pyran which is probably formed from **9** by an electrophilic aromatic substitution under the reaction conditions. The alkyne **9** could easily be hydrogenated to give the alkene **10** using palladium on carbon poisoned with quinoline under a H<sub>2</sub>-atmosphere in acetone at rt for 2.5 h in 79%.<sup>12</sup> The diol *rac*-**11** was synthesised using the *Upjohn* conditions<sup>13</sup> with catalytic amounts of potassium osmate(VI) dihydrate, DABCO and NMO in acetone at 0 °C for 3 d in 72%. Reaction of *rac*-**11** with methanesulfonyl chloride in pyridine at 0 °C and subsequent nucleophilic substitution most probably via a primary formed methanesulfonate using potassium carbonate in methanol at rt for 3 h furnished the desired epoxide *rac*-**12** in 48% yield.<sup>14</sup> Lithium halogen exchange with *n*-BuLi in THF at -78 °C up to rt for 20 h yielded *rac*-**13** in 62% yield.<sup>15</sup> Transformation into the desired *seco*-drug *rac*-**3**

was performed using *Appel* conditions with triphenylphosphine and carbon tetrachloride in 1,2-dichloroethane at 50 °C for 18 h in 85% yield.<sup>16</sup>

At this stage we did not try to transform **3** into **4**, since due to our experience with the *seco*-drugs of ducarmycin SA (**1**) analogues it seemed to be more appropriate to use the *seco*-drug in the *in vitro* assays. Thus, as already mentioned it could be expected that **3** is transformed *in situ* into **4** in the cell culture medium.



**Scheme 1.** Synthesis of racemic *seco*-Drug **3**. a)  $\text{NH}_4\text{OH}$  (aq.),  $\text{ZnCl}_2$ , 190 °C, 4.5 d, 60%; b) phloroglucinol, *p*-TsOH (cat.), *n*-heptanol, reflux, 19 h, 59%; c) NBS,  $\text{ZnCl}_2$ , acetone, -78 °C, 2 h, 59%; d)  $\text{K}_2\text{CO}_3$ , 3-chloro-3-methyl-1-butyne, CuCl (cat.), DMF, rt, 24 h, 68%; e) Pd/C (cat.), quinoline,  $\text{H}_2$  (1 atm), acetone, rt, 2.5 h, 79%; f)  $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$  (cat.), NMO, DABCO, acetone, 0 °C, 3 d, 72%; g) MsCl, pyridine, 0 °C, 30 min then  $\text{K}_2\text{CO}_3$ , MeOH, rt, 3 h, 48%; h) *n*-BuLi, THF, -78 °C to rt, 20 h, 62%; i)  $\text{PPh}_3$ ,  $\text{CCl}_4$ , DCE, 50 °C, 18 h, 85%. *p*-TsOH = *para*-toluenesulfonic acid, NBS = *N*-bromosuccinimide, DMF = dimethylformamide, NMO = *N*-methylmorpholine *N*-oxide, DABCO = 1,4-diazabicyclo[2.2.2]-octane, MsCl = methanesulfonyl chloride, MeOH = methanol, *n*-BuLi = *n*-butyllithium, THF = tetrahydrofuran, DCE = 1,2-dichloroethane.

***In-vitro-cytotoxicity tests:*** The *in-vitro*-cytotoxicity test of the new hybrid **3** was performed with adherent growing cells of the human bronchial carcinoma cell line A549 determining the colony forming ability; *seco*-drug *rac*-**3** showed an IC<sub>50</sub> value of 1040 nm. For comparison the same test was subjected to acronycine **2** which was synthesized according to a known procedure<sup>17</sup> starting from phloroglucinol and anthranilic acid (2-aminobenzoic acid) in three steps showing an IC<sub>50</sub> value of 1140 nm. For an evaluation of the advantage of the new hybrid natural product **3** as a drug candidate its *in vivo* bioactivity including its systemic toxicity will be studied. Moreover, compound **3** allows ample structural variations as the introduction of a tertiary amino functionality to improve water solubility by formation of a salt.

## CONCLUSION

We have designed and biologically evaluated the novel acronycine/*seco*-duocarmycin hybrid natural product **3** by combining parts of acronycine (**2**) with a chloromethyl heterocyclic moiety condensed to a phenol as found in *seco*-duocarmycin. This could form compound **4** *in situ* with the bioactive spirocyclopropyldienone moiety located in **1**. The new hybrid shows a slightly higher cytotoxicity than acronycine (**2**), although it does not contain a double bond which could be transformed *in situ* into an epoxide as anticipated for the mode of action of **2**. Thus, we have developed a new anticancer agent on the basis of the hybrid concept, which might be of interest for further development.

## 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 plates (TLC silica gel 60 F254, Merck) and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Phosphomolybdic acid in MeOH (PMA) or vanillin in methanolic sulphuric acid were used as staining reagents for TLC. UV spectra were recorded in MeCN or MeOH with a Perkin–Elmer Lambda 2 or a JASCO V-630 spectrometer. IR spectra were recorded with a JASCO FT/IR-4100 spectrometer. All substances were applied neat on an ATR unit. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Mercury-300, Unity-300, Inova-500 and Inova-600 spectrometer and a Bruker AMX-300 spectrometer in CDCl<sub>3</sub>. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), coupling constants J in Hertz. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CHCl<sub>3</sub>: δH = 7.24 ppm, δC = 77.36 ppm). Multiplicities of <sup>13</sup>C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured with a Finnigan MAT 95, TSQ 7000 and LCQ instrument. HRMS was performed with a 7 T FTICR-MS APEX IV (Bruker). The

following abbreviations are used in the text: EtOAc = ethyl acetate, PE = petroleum ether (bp 35–60 °C).

**4-Bromo-3-(2,3-dihydroxy-1,1-dimethylpropoxy)-1-hydroxy-5H-benzo[*b*]acridin-12-one (*rac*-11):**

To a solution of alkene **10** (224 mg, 529  $\mu\text{mol}$ , 1.00 equiv.) in acetone (10 mL) and H<sub>2</sub>O (2 mL) was added NMO (92.9 mg, 793  $\mu\text{mol}$ , 1.50 equiv.), DABCO (89.0 mg, 793  $\mu\text{mol}$ , 1.50 equiv.) and K<sub>2</sub>O<sub>8</sub>•2H<sub>2</sub>O (19.5 mg, 52.9  $\mu\text{mol}$ , 0.10 equiv.). The reaction mixture was stirred at 0 °C for 3 d, sat. aq. NaHSO<sub>3</sub>-solution (2 mL) was added, the solution was further stirred for 10 min, then the volatile compounds were evaporated under reduced pressure. The remaining suspension was diluted in 1 N HCl (2 mL) and extracted with EtOAc (4 x 20 mL), the organic layer was dried over MgSO<sub>4</sub> and silica gel (1 g) was added. Removal of the solvents under reduced pressure and purification on silica gel (PE/EtOAc = 1:1 to 100% EtOAc) gave *rac*-**11** (174 mg, 380  $\mu\text{mol}$ , 72%) as a dark orange solid.  $R_f$  = 0.17 (PE/EtOAc = 1:1); <sup>1</sup>H-NMR (301 MHz, DMSO):  $\delta$  = 1.43, 1.47 (s, 6 H, 2 x 1'-CH<sub>3</sub>), 3.47 (ddd,  $J$  = 11.0, 8.0, 5.3 Hz, 1 H, 3'-H<sub>a</sub>), 3.74 (ddd,  $J$  = 8.1, 5.2, 2.9 Hz, 1 H, 2'-H), 3.86 (ddd,  $J$  = 11.0, 6.0, 2.8 Hz, 1 H, 3'-H<sub>b</sub>), 4.49 (t,  $J$  = 5.7 Hz, 1 H, 3'-OH), 5.11 (d,  $J$  = 5.2 Hz, 1 H, 2'-O-H), 6.63 (s, 1 H, 2-H), 7.38–7.53 (m, 1 H, 8-H), 7.61 (dd,  $J$  = 11.1, 4.0 Hz, 1 H, 9-H), 7.93 (d,  $J$  = 8.4 Hz, 1 H, 7-H), 8.15 (d,  $J$  = 8.2 Hz, 1 H, 10-H), 8.50 (s, 1 H, 6-H), 8.88 (s, 1 H, 11-H), 10.54 (s, 1 H, NH), 14.26 (s, 1 H, 1-OH); <sup>13</sup>C-NMR (75 MHz, DMSO):  $\delta$  = 22.0, 24.2 (2 x 1'-CH<sub>3</sub>), 62.0 (C-3'), 76.9 (C-2'), 86.0 (C-1'), 90.4 (C-4), 99.5 (C-2), 103.5 (C-12a), 113.6 (C-6), 119.1 (C-5a), 124.6 (C-8), 126.2 (C-7), 126.6 (C-11), 128.0 (C-6a), 128.7 (C-9), 129.3 (C-10), 135.8 (C-10a), 136.9 (C-11a), 140.5 (C-4a), 159.4 (C-3), 162.5 (C-1), 181.5 (C-12); HRMS (ESI)  $m/z$  calcd. for C<sub>22</sub>H<sub>20</sub>BrNO<sub>5</sub>: 454.0296 [M-H<sup>+</sup>]<sup>-</sup>, found: 454.0292.

**4-Bromo-1-hydroxy-3-(1-methyl-1-oxiranylethoxy)-5H-benzo[*b*]acridin-12-one (*rac*-12):** A solution of compound *rac*-**11** (347 mg, 756  $\mu\text{mol}$ , 1.00 equiv.) in pyridine (13 mL) was stirred at 0 °C for 30 min, then mesyl chloride (117  $\mu\text{L}$ , 1.51 mmol, 2.00 equiv.) was added and stirring was continued for 1 h. After evaporation of the volatile compounds under reduced pressure the residue was dissolved in MeOH (20 mL), then K<sub>2</sub>CO<sub>3</sub> (523 mg, 3.78 mmol, 5.00 equiv.) was added and the dark red solution was stirred for 3 h at rt. The solvent was evaporated at rt, ice-cold 1 N HCl (5 mL) was added and the aqueous layer extracted with EtOAc (3 x 10 mL). After drying over Na<sub>2</sub>SO<sub>4</sub> silica gel (2 g) was added and the volatile compounds were removed under reduced pressure to give *rac*-**12** (160 mg, 363  $\mu\text{mol}$ , 48%) as an orange solid after purification on silica gel (PE/EtOAc = 4:1 to 3:1 to 2:1).  $R_f$  = 0.71 (PE/EtOAc = 2:1); <sup>1</sup>H-NMR (301 MHz, DMSO):  $\delta$  = 1.32, 1.50 (s, 6 H, 2 x 1'-CH<sub>3</sub>), 2.84 (dd,  $J$  = 4.7, 2.8 Hz, 1 H, 3'-H<sub>a</sub>), 2.90 (t,  $J$  = 4.5 Hz, 1 H, 3'-H<sub>b</sub>), 3.35 (dd,  $J$  = 4.3, 2.8 Hz, 1 H, 2'-H), 6.67 (s, 1 H, 2-H), 7.46 (d,  $J$  = 7.9 Hz, 1 H, 8-H), 7.59 (d,  $J$  = 7.2 Hz, 1 H, 9-H), 7.91 (d,  $J$  = 8.3 Hz, 1 H, 7-H), 8.13 (d,  $J$  = 8.3 Hz, 1 H, 10-H), 8.48 (s, 1 H, 6-H), 8.86 (s, 1 H, 11-H), 10.53 (s, 1 H, NH), 14.26 (s, 1 H, 1-OH); <sup>13</sup>C-NMR (75 MHz, DMSO):  $\delta$  = 20.1, 25.0 (2 x 1'-CH<sub>3</sub>), 44.6 (C-3'), 56.5 (C-2'), 82.4 (C-1'), 89.6 (C-4), 98.7 (C-2),

103.5 (C-12a), 113.6 (C-6), 119.1 (C-5a), 124.5 (C-8), 126.2 (C-7), 126.5 (C-11), 127.9 (C-6a), 128.7 (C-9), 129.3 (C-10), 135.8 (C-10a), 136.8 (C-11a), 140.4 (C-4a), 158.8 (C-3), 162.7 (C-1), 181.5 (C-12); HRMS (ESI)  $m/z$  calcd. for  $C_{22}H_{18}BrNO_4$ : 438.0346  $[M-H]^+$ , found: 438.0330.

**5-Hydroxy-1-(hydroxymethyl)-2,2-dimethyl-1,2-dihydrobenzo[*b*]furo[3,2-*h*]acridin-6(13*H*)-one**

**(*rac*-13)**: Epoxide *rac*-12 (59.4 mg, 135  $\mu$ mol, 1.00 equiv.) was dissolved in THF (10 mL), cooled to  $-78$  °C and stirred for 15 min at that temperature. *n*-BuLi (205  $\mu$ L, 472  $\mu$ mol, 3.50 equiv., 2.5 M in hexane) was added at  $-78$  °C and the reaction was allowed to warm to rt within 20 h. Sat. aq.  $NH_4Cl$ -sol. (2 mL) was added, the aqueous layer extracted with EtOAc (3 x 20 mL), the organic layer dried over  $MgSO_4$ , silica gel (250 mg) was added and the volatile compounds were removed under reduced pressure. *rac*-13 (30.3 mg, 83.9  $\mu$ mol, 62%) was obtained after purification on silica gel (PE/EtOAc = 3:1  $\rightarrow$  2:1) as an orange solid.  $R_f$  = 0.21 (PE/EtOAc = 2:1);  $^1H$ -NMR (301 MHz, DMSO):  $\delta$  = 1.42, 1.50 (s, 6 H, 2 x 2- $CH_3$ ), 3.45 (dd,  $J$  = 8.0, 4.4 Hz, 1 H, 1-H), 3.73 (t,  $J$  = 9.3 Hz, 1 H, 1'- $H_a$ ), 3.93 (dd,  $J$  = 10.5, 4.2 Hz, 1 H, 1'- $H_b$ ), 5.96 (s, 1 H, 1'-OH), 6.01 (s, 1 H, 4-H), 7.42 (ddd,  $J$  = 8.0, 6.7, 1.1 Hz, 1 H, 10-H), 7.58 (ddd,  $J$  = 8.3, 6.7, 1.2 Hz, 1 H, 9-H), 7.85 (s, 1 H, 12-H), 7.95 (d,  $J$  = 8.1 Hz, 1 H, 11-H), 8.11 (d,  $J$  = 8.3 Hz, 1 H, 8-H), 8.86 (s, 1 H, 7-H), 11.49 (s, 1 H, NH), 14.53 (s, 1 H, 5-OH);  $^{13}C$ -NMR (75 MHz, DMSO):  $\delta$  = 22.0, 28.4 (2 x 2- $CH_3$ ), 51.0 (C-1), 60.1 (1- $CH_2$ ), 89.9 (C-4), 90.1 (C-2), 102.4 (C-5a), 102.6 (C-13b), 111.4 (C-12), 119.5 (C-12a), 124.1 (C-10), 126.2 (C-7), 126.3 (C-11), 127.7 (C-11a), 128.4 (C-9), 129.3 (C-8), 135.7 (C-7a), 136.9 (C-6a), 139.8 (C-13a), 165.0 (C-3a), 165.3 (C-5), 180.9 (C-6); HRMS (ESI)  $m/z$  calcd. for  $C_{22}H_{19}NO_4$ : 360.1241  $[M-H]^+$ , found: 360.1236.

**1-(Chloromethyl)-5-hydroxy-2,2-dimethyl-1,2-dihydrobenzo[*b*]furo[3,2-*h*]acridin-6(13*H*)-one**

**(*rac*-3)**: Alcohol *rac*-13 (9.30 mg, 25.7  $\mu$ mol, 1.00 equiv),  $PPh_3$  (20.3 mg, 77.2  $\mu$ mol, 3.0 equiv.) and  $CCl_4$  (23.0  $\mu$ L, 232 mmol, 9.00 equiv.) were dissolved in DCE (6 mL) and stirred for 18 h at 50 °C in a pressure flask. Silica gel (50 mg) was added, removal of the solvent under reduced pressure and purification on silica gel (PE/EtOAc = 10:1) gave *rac*-3 (8.31 mg, 21.9  $\mu$ mol, 85%) as an orange solid.  $R_f$  = 0.71 (PE/EtOAc = 2:1);  $^1H$ -NMR (600 MHz, DMSO):  $\delta$  = 1.42, 1.71 (s, 6 H, 2 x 2- $CH_3$ ), 3.77 (dd,  $J$  = 6.9, 2.5 Hz, 1 H, 1-H), 3.95 (dd,  $J$  = 12.1, 2.5 Hz, 1 H, 1'- $H_a$ ), 4.01 (dd,  $J$  = 12.0, 7.0 Hz, 1 H, 1'- $H_b$ ), 6.05 (s, 1 H, 4-H), 7.46 (m<sub>c</sub>, 1 H, 10-H), 7.62 (m<sub>c</sub>, 1 H, 9-H), 8.00 (d,  $J$  = 8.7 Hz, 1 H, 11-H), 8.09 (s, 1 H, 12-H), 8.16 (d,  $J$  = 8.4 Hz, 1 H, 8-H), 8.90 (s, 1 H, 7-H), 11.12 (s, 1 H, NH), 14.63 (s, 1 H, 5-OH);  $^{13}C$ -NMR (126 MHz, DMSO):  $\delta$  = 21.6, 28.7 (2 x 2- $CH_3$ ), 43.0 (C-1'), 48.7 (C-1), 89.9 (C-4), 90.3 (C-2), 100.4 (C-13b), 102.4 (C-5a), 112.0 (C-12), 119.6 (C-12a), 124.3 (C-10), 126.2 (C-7), 126.4 (C-11), 127.7 (C-11a), 128.5 (C-9), 129.3 (C-8), 135.6 (C-7a), 137.1 (C-6a), 139.7 (C-13a), 165.2 (C-3a), 165.6 (C-5), 181.0 (C-6); HRMS (ESI)  $m/z$  calcd. for  $C_{22}H_{19}ClNO_3$ : 378.0902  $[M-H]^+$ , found: 378.0886.

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