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A direct transformation of *O*-silyl groups into *O*-trichloroacetates. A novel synthetic approach to protein kinase C ligands: 1-oleoyl-2-acetyl- and 1-hexadecyl-2-acetyl-*sn*-glycerols

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Abstract—A fluoride ion-promoted direct esterification of *tert*-butyldimethylsilyl- (TBDMS), or triisopropylsilyl (TIPS)-protected glycerol derivatives by means of trichloroacetic anhydride (TCAA), followed by removal of the trichloroacetyl transient protection, provides a new, efficient entry to stereochemically pure 1-oleoyl-2-acetyl- and 1-*O*-hexadecyl-2-acetyl-*sn*-glycerols.

1. Introduction

It has only recently become apparent that 1,2-diacyl-*sn*-glycerols (DAG) and their 1-*O*-alkyl-2-acyl-*sn*-isosteres (ALAG), when transiently generated within cells from various carrier-molecules (e.g., phospholipids, triglycerides, etc.), can modulate a broad spectrum of protective or physiopathological processes in living organisms via signal transduction pathways.[1] Due to this, the aforementioned classes of diglycerides (DG) emerged as synthetic targets of considerable importance in carbohydrate,[2] nucleic acid,[3] and lipid research,[4,5] relevant to rational drug design.[6] Growing interest in lipid mediators and their conjugates caused an increasing demand for configurationally pure 1-oleoyl-2-acetyl- and 1-*O*-hexadecyl-2-acetyl-*sn*-glycerol as valuable precursors to various bioactive natural products[7,8] and specific effectors of protein kinase C (PKC).[8] The latter aspect is of particular importance for developing new biochemical and medicinal diagnostics and in structure–activity relationship studies of potential therapeutics targeting PKC.[9]

Despite the apparent structural simplicity, synthesis of unsymmetrical 1,2-diacylglycerols has repeatedly been shown to be a complicated task since incorporation of two different substituents at the primary versus secondary glycerol position calls for an extensive use of protecting groups, which must be removable under conditions that do not provoke acyl scrambling and in the case of unsaturated derivatives, are also compatible with the presence of double bonds.[5,10] Unfortunately, problems often arise at the end of synthesis as most of the protecting systems available to date (e.g., levulinate,[11] benzyl,[12] trityl,[9,13] 2,2,2-trichloroethoxycarbonyl,[14] 9-phenylxanthen-9-yl,[15] etc.) require deblocking conditions that either preclude admission to conjugates with unsaturated or acid/base-sensitive replacements,[5] or trigger undesirable molecular rearrangements (e.g., acyl migration, racemization, etc.) after exposure of a free hydroxyl group of the glycerol backbone.[5,16]

The growing recognition of the common protection–deprotection protocols as sources of acute preparative complications,[5,11,17] turned our attention to silyl groups as alternative protecting groups. Although organosilicon derivatives have found numerous applications in the synthesis of complex organic compounds,[18] they have not been exploited to any significant extent in glycerolipid chemistry since the cleavage conditions are frequently detrimental to acid-,[19] base-,[20] or

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oxidation/reduction-susceptible substrates,[21] or promote an acyl migration process.[20] A reagent recommended for the deprotection of terminal TBDMS–ethers of DAG without acyl migration,[22] *N*-bromosuccinimide,[23] proved to be incompatible with unsaturated fatty acid residues due to its powerful brominating properties. Another reagent, pyridinium *p*-toluenesulfonate in CH_2Cl_2–CH_3OH (2:1 v/v) significantly suppressed the acyltropy (acid, base, or heat initiated migration of an acyl group[24]) during desilylation of ALAG,[25] but was shown to be impractically slow (reaction time: up to 14 days at 0 °C).

One should also note that none of the above methodologies provides direct access to the DG needed after deprotection. Instead, these procedures involve work-up and a painstaking chromatography[5,22,25] to separate the target compounds from by-products. However, such additional operations often contribute to side-reactions or decomposition of labile acylglycerols.[5,24]

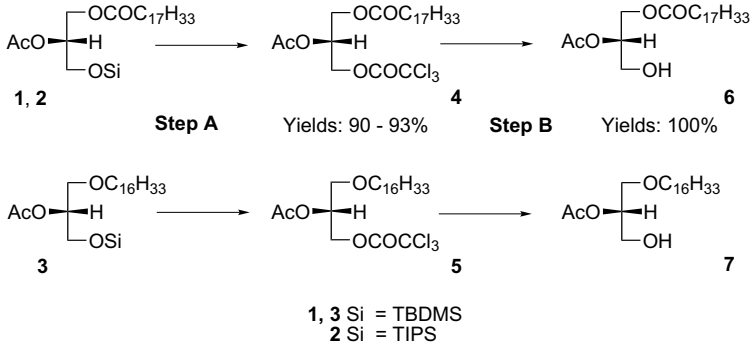
In this letter, we report that treatment of 1-oleoyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl- **1**, 1-oleoyl-2-acetyl-3-*O*-triisopropylsilyl- **2**, or 1-*O*-hexadecyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerols **3** with trichloroacetic anhydride in the presence of triethylamine tris(hydrofluoride) (TEA·3HF) effects a direct transformation between silyl and trichloroacetyl protecting groups. Since the removal of a trichloroacetyl moiety can be carried out quantitatively and without additional purification, thus eliminating drawbacks inherent to deprotection of their silyl-counterparts, this may constitute a novel strategy for the synthesis of configurationally homogeneous protein kinase C ligands, namely 1-oleoyl-2-acetyl- **6** and 1-*O*-hexadecyl-2-acetyl-*sn*-glycerols **7** (Scheme 1), or related compounds.

To implement this protocol, reaction conditions for a direct trichloroacetylation of compounds **1**–**3** (Scheme 1, step A) bearing two silyl protecting groups of most common use in general organic synthesis,[18] TBDMS and TIPS, were investigated employing different solvents, ratio of reactants, etc. The best results were achieved when compounds **1**–**3** were treated under argon with neat TCAA (9.0 equiv) and TEA·3HF (2.0 equiv) in a tightly stoppered glass ampoule at 80 °C for 2 h. This produced quantitatively and in a highly chemo- and regiospecific manner (>99%, ^1H and ^{13}C NMR spectroscopy) trichloroacetates **4** and **5**, which were isolated in 90–93% yields after flash column silica gel chromatography. The obtained trichloroacetyl derivatives **4** and **5** can either be subjected directly to subsequent transformations, or stored for several months (−20 °C, under argon) without detectable alterations of their spectral characteristics (^1H and ^{13}C NMR spectroscopy).

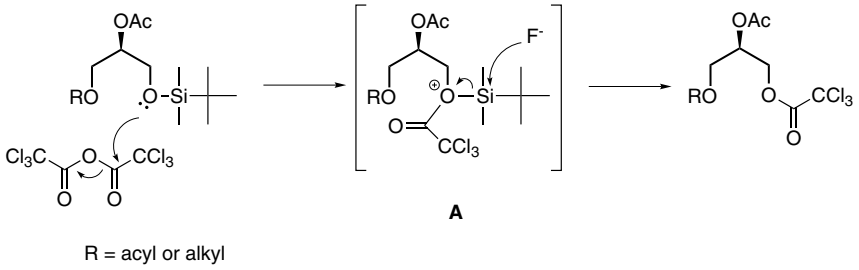
Regarding the scope and limitations of this particular chemistry, some additional observations are pertinent. The rate of replacement of the silyl groups by a trichloroacetyl moiety was not appreciably influenced by electronic features or the type of molecular fragments present in **1**–**3** (e.g., unsaturated acyl, various alkyl groups). Trimethylsilyl derivatives underwent esterification at comparable rates to those of TBDMS and TIPS ethers. The reactions in organic solvents were considerably slower (e.g., in $CHCl_3$; reaction time ~48 h) or produced complex reaction mixtures (e.g., reactions in THF). The rate of trichloroacetylation remained practically within the same range of magnitude upon replacement of TEA·3HF by tetra-*n*-butylammonium fluoride (TBAF·$3H_2O$). In the latter case, however, ^1H and ^{13}C NMR analysis revealed that regioselectivity was eroded due to acyl migration (5–10%), triggered probably by the substantial amounts of free trichloroacetic acid generated from TCAA in the presence of water. To suppress this process, a larger excess of TCAA (up to 15 equiv) was required. Although trifluoroacetic anhydride could be used as a substitute for TCAA, the trifluoroacetyl derivatives were less convenient to work with as they decomposed during column chromatography.

It was interesting to note that for TBDMS derivatives **1** and **3** the reactions could be carried out without fluoride ion present, by using tetra-*n*-butylammonium trichloroacetate with 2 equiv of TCAA. Unfortunately, these reactions were rather slow (e.g., in $CHCl_3$ at rt, ca. 24 h; ~90% conversion) and failed for TIPS derivatives (<5% conversion after 24 h; TLC).

On the basis of the above data we can tentatively formulate a mechanism which involves an electrophilic attack



Scheme 1. Reagents and conditions: (step A) $Et_3N·3HF$ (2.0 equiv)/$(CCl_3CO)2O$ (9.0 equiv), no solvent, 80 °C/2 h; (step B) pyridine (50 equiv)/MeOH (500 equiv), THF, rt/3 h.



Scheme 2.

by TCAA to form an intermediate of type **A**, followed by a nucleophilic attack by the fluoride ion on the silicon (Scheme 2). This rationalizes the replacement of the silyl protection by trichloroacetyl without migration of the acetyl group. Since no bond breaking takes place at the stereogenic C2-center, the transformation is supposed to be stereospecific and to occur with retention of configuration. The observed exclusive formation of trifluoroacetates **4** or **5** with defined stereochemistry (see Experimental) and the lack of an intramolecular acyl scrambling, are in agreement with this hypothesis.

An alternative mechanism comprising a nucleophilic attack by a trichloroacetate anion on silicon, seems to be less likely as fluoride ion is orders of magnitude more effective as a nucleophile for silicon then carboxylates. This is also consistent with the reactions carried out in the absence of fluoride (see above).

As a final stage of this investigation, the trichloroacetates **4** and **5** were converted into 2-acetylglycerols **6** and **7**, respectively (Scheme 1, step B). Due to the high electrophilicity of the carbonyl center of trichloroacetyl derivatives, this could be carried out selectively even in the presence of an acetyl group, by treating compounds **4** and **5** in THF with pyridine (50 equiv) and methanol (500 equiv) at room temperature. The reactions were quantitative (completion within 3 h) and after removal of the volatile products, diglycerides **6** and **7** of purity >99% (^{1}H and ^{13}C NMR spectroscopy) could be obtained without any additional purification.

In conclusion, we have developed an efficient synthetic strategy based on a novel transformation of silyl ethers into trichloroacetyl derivatives to afford functionalized glyceride synthons **4** and **5** as convenient storage forms (protection of 3-hydroxyl groups as trichloroacetyl esters should prevent scrambling of the acyl moiety) or intermediate frameworks from which protein kinase C ligands (e.g., **6** and **7**) can be retrieved directly without recourse to any additional purification techniques. The method seems to be general and will probably be applicable to the synthesis of other lipid derivatives.

The main features of this new protocol are: (i) highly regioselective and quantitative generation under mild conditions of 1,2-diacyl- **6** and 1-alkyl-2-acyl-3-*sn*-glycerols **7** bearing unsaturated or saturated alkyl chain; (ii) the produced compounds **6** and **7** are of high purity, which alleviates problems of their additional processing, thus eliminating potential sources for acyl migration and other side-reactions; (iii) the method introduces silyl and trichloroacetyl groups as versatile protecting functionalities in the synthesis of bioactive lipid mediators; (iv) it makes use of commercially available reactants and can easily be scaled up.

2. Experimental

2.1. Starting substrates 1–3

Obtained in two steps via consecutive silylation and acylation of chiral monoglycerides[26] according to standard procedures[22,27] or as described elsewhere.[28] The synthesized compounds have been characterized by ^{1}H- and ^{13}C NMR spectroscopy, and their purity (>99%) assessed by ^{1}H NMR.

2.1.1. 1-Oleoyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 1. Colorless oil; R_f (pentane–toluene–EtOAc = 40:50:10, v/v/v) = 0.62; $[\alpha]_D^{20}$ +9.75 (*c* 11.05, $CHCl_3$). Found: C, 67.88; H, 11.08%. $C_{29}H_{56}O_5Si$ (512.84) requires C, 67.92; H, 11.01%.

2.1.2. 1-Oleoyl-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol 2. Colorless oil; R_f (pentane–toluene–EtOAc = 40:50:10, v/v/v) = 0.61; $[\alpha]_D^{20}$ +11.28 (*c* 9.87, $CHCl_3$). Found: C, 69.20; H, 11.30%. $C_{32}H_{62}O_5Si$ (554.92) requires C, 69.26; H, 11.26%.

2.1.3. 1-*O*-Hexadecyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 3. Colorless oil; R_f (pentane–toluene–EtOAc = 40:50:10, v/v/v) = 0.58; $[\alpha]_D^{20}$ +4.51 (*c* 14.60, $CHCl_3$). Found: C, 68.67; H, 11.87%. $C_{27}H_{56}O_4Si$ (472.82) requires C, 68.59; H, 11.94%.

2.2. General procedure for the direct conversion of silyl ethers 1–3 into trichloroacetates 4 and 5 (step A)

A mixture of the starting silyl ether **1**–**3** (1.00 mmol), trichloroacetic anhydride (1.644 mL, 9.00 mmol) and triethylamine tris(hydrofluoride) (0.326 mL, 2.00 mmol) was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath) for 2 h. The system was taken in toluene–ethyl acetate (98:2, v/v; 5 mL) and the target trichloroacetyl derivative **4** or **5** was isolated in pure state (purity >99%, ^{1}H NMR spectroscopy) by flash column chromatography (silica gel; mobile phase: toluene–ethyl acetate = 98:2, v/v).

2.2.1. 1-Oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (obtained from 1) 4. Yield: 0.506 g (93%, colorless oil); R_f (pentane–toluene–EtOAc = 40:50:10, v/v/v) = 0.56; $[\alpha]_D^{20}$ −0.40 (*c* 7.18, $CHCl_3$). Found: C, 55.00; H, 7.70; Cl, 19.73%. $C_{25}H_{41}O_6Cl_3$ (543.95) requires C, 55.20; H, 7.60; Cl, 19.55%.

2.2.2. 1-Oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (obtained from 2) 4. Yield: 0.489 g (90%, colorless oil); $[\alpha]_D^{20}$ −0.42 (*c* 9.43, $CHCl_3$); all other physicochemical and spectral characteristics are identical with those of the previous product.

2.2.3. 1-*O*-Hexadecyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (obtained from 3) 5. Yield: 0.464 g (92%, colorless oil); R_f (pentane–toluene–EtOAc = 40:50:10, v/v/v) = 0.54; $[\alpha]_D^{20}$ −5.81 (*c* 11.81, $CHCl_3$). Found: C, 54.82; H, 8.27; Cl, 21.00%. $C_{23}H_{41}O_5Cl_3$ (503.93) requires C, 54.82; H, 8.20; Cl, 21.11%.

2.3. General procedure for the synthesis of diglycerides 6 and 7 (step B)

To a solution of **4** or **5** (1.00 mmol) in tetrahydofuran (5.0 mL), a mixture of pyridine (4.0 mL, 50 mmol) and methanol (20.3 mL, 500 mmol) was added and the reaction system was left at room temperature for 3 h. Solvents were evaporated under reduced pressure (bath temp. 50 °C) and the residue was kept under high vacuum at room temperature for 2–3 h to give the unprotected diglyceride **6** or **7** (purity >99%, ^{1}H NMR spectroscopy).

2.3.1. 1-Oleoyl-2-acetyl-*sn*-glycerol (obtained from 1 via 4) 6. Overall yield (calculated on **1**): 0.370 g (93%, colorless oil); R_f (toluene–EtOAc = 80:20, v/v) = 0.24; $[\alpha]_D^{20}$ −5.42 (*c* 5.07, $CHCl_3$). Found: C, 70.01; H, 10.60%. $C_{23}H_{42}O_5$ (398.58) requires C, 69.31; H, 10.62%.

2.3.2. 1-Oleoyl-2-acetyl-*sn*-glycerol (obtained from 2 via 4) 6. Yield (calculated on **4**): 0.398 g (100%, colorless oil); $[\alpha]_D^{20}$ −5.33 (*c* 9.50, $CHCl_3$); all other physicochemical and spectral characteristics are identical with those of the previous product.

2.3.3. 1-*O*-Hexadecyl-2-acetyl-*sn*-glycerol (obtained from 5) 7. Yield: 0.358 g (100%, white solid, mp 35.5–36.0 °C, from pentane); R_f (toluene–EtOAc = 80:20, v/v) = 0.23; $[\alpha]_D^{20}$ −5.44 (*c* 2.39, $CHCl_3$); lit.[29] $[\alpha]_D^{20}$ −11.1 (*c* 0.4, $CHCl_3$).

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