Semisynthesis of Ingenol 3-Angelate (PEP005): Efficient Stereoconservative Angeloylation of Alcohols

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Dedicated to the memory of Professor Horst Prinzbach

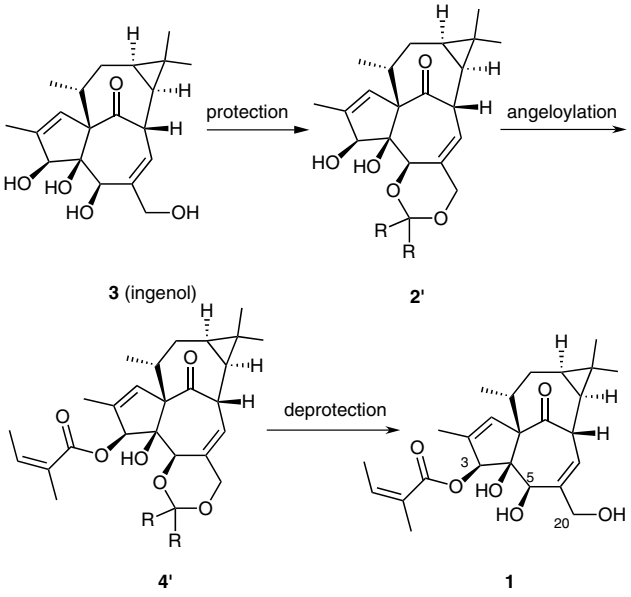
Abstract: A high-yielding method was developed for the preparation of ingenol 3-angelate (PEP005, ingenol mebutate) via the corresponding 5,20-acetonide without concomitant isomerization of the angelate (*Z*-form) to the corresponding tiglate (*E*-form). The general scope of the stereoconservative esterification method was further evaluated on several different alcohols, giving the angelates in up to quantitative yield without isomerization to the tiglate.

Key words: ingenol, ingenol 3-angelate, PEP005, angeloylation, isomerization, tiglate

Ingenol 3-angelate (**1**, PEP005, ingenol mebutate, Picato®) is a cell death inducer and a protein kinase C activator recently approved by FDA for the treatment of actinic (or solar) keratosis, a disease stage associated with sun exposure which potentially can develop into skin cancer.[1] Ingenol 3-angelate has a dual action by induction of necrosis followed by a PKC-driven immune response and wound healing.[2] The sap from *Euphorbia peplus* has proven effective against human non-melanoma skin cancers and has also been used for self-treatment of skin cancer and solar keratosis.[3] Ingenol 3-angelate was originally isolated from various *Euphorbia* species, and particularly from *E. peplus* by extraction followed by chromatography.[4] According to this procedure, extraction of 17 kg of fresh *E. peplus* afforded 7 g of a crude oil, which was purified by HPLC, giving the ingenol 3-angelate in a low yield. Therefore, an alternative process was sought.

We chose ingenol as a starting point as it is a natural product which is accessible from the widely available seeds of *Euphorbia lathyris*.[5] During the extraction, the various ingenol esters present are hydrolyzed, therefore, the amount of isolated ingenol is increased. In this letter, we present the first semisynthesis of ingenol 3-angelate starting from ingenol (**3**).

The synthetic strategy is outlined in Scheme 1. Due to the different reactivity of the four alcohol groups in ingenol (**3**), it is possible to selectively block the 5,20-diol and keep the 3,4-diol unprotected. Steric hindrance of the 4-OH allows a regioselective esterification of the 3-OH group. Finally, deprotection will give the target molecule, ingenol 3-angelate (**1**).



Scheme 1 Synthetic strategy

Angeloylation is a long standing synthetic challenge because it is often accompanied by the formation of variable amounts of thermodynamically more stable tiglate by-products (*E*-form).[6] We require a stereoconservative[7] esterification as the isomerization will cause mixtures often hard to separate and low yields as a consequence. In the literature, three general methods for angeloylation are described. (i) Carbodiimide coupling reagents such as DCC and EDCI have been used for this conversion.[8] By solely using carbodiimide coupling reagents, the coupling reactions are sluggish, while addition of reversible nucleophilic catalysts often leads to tiglates as main products. (ii) Angelic acid (**6**) can be converted into angeloyl chloride (**7**), which is reacted with an alcohol, but this method is delicate to perform without isomerization during the conversion into the acid chloride.[9,10] (iii) In 1991, Greene et al. adopted the Yamaguchi mixed anhydride method for the preparation of an angelate ester by in situ generation of the mixed anhydride from 2,4,6-trichlorobenzoyl chloride and angelic acid in the presence of triethylamine.[11]

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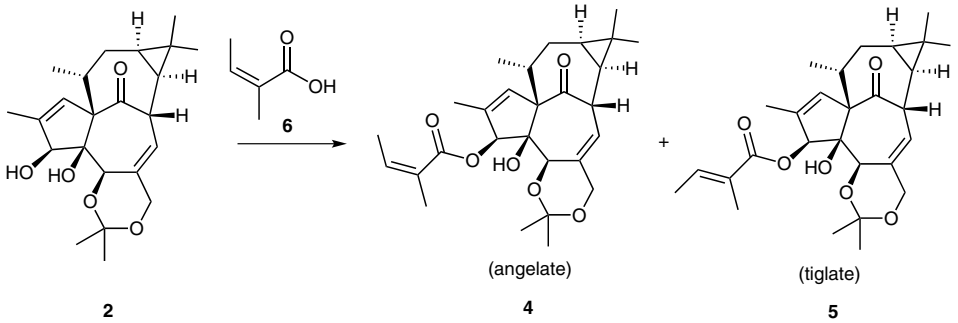
Table 1 Reaction of Angelic Acid (**6**) with **2** in the Presence of Carbodiimides [Coupling Strategy (i)][a]



2 **4** **5**

Entry	Coupling reagent	Catalyst	Time	Conv.[b]	Ratio **4/5**[b]
1	DCC	–	2 d	2%	99:1
2	EDCI	–	2 d	0%	–
3	DCC	DMAP	2 d	75%	15:85
4	EDCI[c]	DMAP	1 d	55%	4:96

[a] Equimolar amounts of ingenol-5,20-acetonide and angelic acid were dissolved in $CDCl_3$ (0.15 M). DMAP (2 equiv) was added before the dropwise addition of a solution of the coupling reagent (1–2 equiv) in the solvent. The progress of the reaction was monitored by TLC and ^{1}H NMR spectroscopy.
[b] Conversions and ratios of angelate **4**/tiglate **5** were estimated from ^{1}H NMR of the crude reaction mixtures.
[c] CH_2Cl_2 was used as solvent.

This appears to be the most widely used protocol for the preparation of angelate esters.[12]

We started by preparing the known ingenol 5,20-acetonide (**2**), following Hecker's protocol.[13] Due to its high crystallinity, we found that the crude product from the reaction can be purified simply by crystallization without any chromatography. This finding is very suitable for large-scale production.

For angeloylation of **2**, we tried the coupling strategy (i) using DCC or EDCI (Table 1). It turned out that almost no desired product **4** (≤2%) was obtained in the absence of a catalyst (Table 1, entries 1 and 2). Instead, the angelic acid was converted into angelic anhydride (**9**), which was proven highly unreactive under the conditions used. However, by using DMAP as a catalyst, the reaction was fast and a high conversion was achieved, albeit giving tiglate **5** as the main product (Table 1, entries 3 and 4). Interestingly, tiglic acid and **2** were coupled under the same conditions (DCC–DMAP), giving exclusively ingenol 3-tiglate in 84% yield. The isomerization during angeloylation can probably be attributed to a reversible Michael addition of the acylation catalyst such as DMAP or pyridine to the *O*-acylurea intermediate or to the *N*-acylpyridinium salt providing a single rotatable bond.[14] As a result, the thermodynamically more stable tiglate isomer is obtained. The extent of isomerization appears to depend on the reaction rate of the angeloylation. Thus, the faster the esterification, the lesser isomerization occurs.

We then investigated the angeloyl chloride approach (ii) by following Beeby's protocol (Table 2).[9] The reaction did not proceed without any base added (Table 2, entry 1). Again, nucleophilic catalysts such as pyridine and DMAP were tried (Table 2, entries 3 and 4), but as expected, tiglate **5** was obtained as the main product. We explored the use of a strong base[10k] to activate compound **2** by deprotonation of the 3-OH. Indeed, when LHMDS was used, we observed reasonable conversion with a high angelate to tiglate ratio (Table 2, entry 2). Unfortunately, the reaction was not clean but accompanied by some impurities.

Table 2 Reaction of Angeloyl Chloride (7) with **2** [Coupling Strategy (ii)][a]

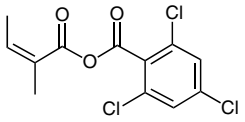
Entry	Base	Solvent	Time	Conv. **4/5**[b]	**4/5** ratio[b]
1	–	THF	1 d	–	–
2	LHMDS	THF	1 d	60%	97:3[c]
3	pyridine	pyridine	2 d	75%	4:96
4	DMAP	THF	2 d	55%	4:96

[a] Ingenol-5,20-acetonide was dissolved in the appropriate solvent at r.t. For the reactions conducted in the presence of a base, the base (1.15 equiv LHMDS, large excess of pyridine, 1.5 equiv DMAP) was added before the addition of angeloyl chloride (1.5 equiv in entries 1, 3 and 4 and 1.2 equiv in entry 2).
[b] Conversions and ratios of angelate **4**/tiglate **5** were estimated from ^{1}H NMR of the crude reaction mixtures.
[c] The ratio reflects the isomerization of angeloyl chloride to tigloyl chloride during storage.

Our third choice was Greene's protocol (iii),[11] the modified one-pot Yamaguchi esterification (Table 3). As the original protocol was followed, not only excess angelic

acid was required (Table 3, entry 1), but also unacceptable isomerization took place. The excess of reagent was expected to lead to purification problems. By using isolated pure mixed anhydride **8**, the reaction proceeded at 100 °C for 22 hours, giving a reasonable yield of 74% (Table 3, entry 2). However, 2–3% of compound **5** in the chromatographically purified product was detected by ^{1}H NMR. We conducted the reaction in the presence of $NaHCO_3$,[12m,n] giving **4** in a comparable yield (76%) and with a negligible amount of **5** produced (Table 3, entry 3). We were still not satisfied with this procedure. Firstly, following Ley's protocol for preparation of **8**,[12m] only 49% yield of the desired anhydride was obtained, even though 10 equivalents of 2,4,6-trichlorobenzoyl chloride were used. Reproducibility of the procedure was variable due to the unstable mixed anhydride **8**, which constantly underwent disproportionation, producing a mixture of angelic anhydride (**9**), 2,4,6-trichlorobenzoic anhydride and **8**. This phenomenon has previously been reported in the literature.[15] Furthermore, under the same reaction conditions as for the mixed anhydride **8**, angelic anhydride proved to be unreactive. Not surprisingly, in the one-pot procedure, it is common that 5–10 equivalents, and in some cases even 30–50 equivalents of angelic acid were needed for completion of the reaction. Secondly, the yield was still not satisfactory for a reaction involving an expensive alcohol such as ingenol. Thus, a more efficient method was needed.

Table 3 Reaction of Mixed Anhydride **8** with **2** [Coupling Strategy (iii)][a,b,c]



8

Entry	Base	Time	Isolated yield	**4/5** ratio[d]
1[a]	–	48 h	49%	99:4
2[b]	–	22 h	74%	97:3
3[c]	$NaHCO_3$	22 h	76%	>99:1

[a] The mixed anhydride was prepared from angelic acid (2 equiv), 2,4,6-trichlorobenzoyl chloride (2 equiv) and triethylamine (2 equiv) in toluene. Ingenol 5,20-acetonide (1 equiv) was added, and the mixture was heated at 100 °C with stirring.
[b] A solution of purified mixed anhydride (1.25 equiv), ingenol 5,20–acetonide (1 equiv) was heated at 100 °C with stirring.
[c] A mixture of purified mixed anhydride (1.25 equiv), ingenol 5,20–acetonide (1 equiv) and $NaHCO_3$ (1.5 equiv) was heated at 100 °C with stirring.
[d] The angelate/tiglate ratios were determined by ^{1}H NMR of isolated products.

Angelic anhydride (**9**) is commercially available, but it has been reported by several research groups to display insufficient reactivity towards alcohols.[11,12n] We observed no conversion without catalyst at room temperature (entry 1) and mainly isomerization using pyridine or DMAP (entries 2 and 3) as shown in Table 4. We wondered whether it was feasible to use a strong base to increase the nucleophilicity of ingenol acetonide **2** to facilitate the reaction with angelic anhydride (**9**). Thus, a series of bases were investigated (Table 4). For the angeloylation of **2**, we used commercially available **9** which contains approximately 3% angelic-tiglic mixed anhydride. Initially, we tested three alkali metal hexamethyldisilazane bases (LHMDS, NaHMDS, and KHMDS) with good results (Table 4, entries 4–6). Among the three bases, LHMDS was superior (Table 4, entry 4). The reaction was proven to be fast and complete in ten minutes at 10–15 °C, while by using NaHMDS and KHMDS, the reactions were slower. The reason could be that angelic anhydride is activated by the lithium ion with its high charge density being closely associated with the two carbonyls as has been described for other O–Li–O and O–Li–N systems.[16] To avoid tiglate contamination, we decided to prepare pure angelic anhydride. Thus, it was found that angelic acid, containing 0.5% tiglic acid, could be reacted with a half equivalent of DCC in dichloromethane to furnish angelic anhydride in essentially quantitative yield with only a trace of angelic-tiglic mixed anhydride. The product was conveniently purified by chromatography without any isomerization or degradation. With nearly pure angelic anhydride in hand, **4** was prepared in 86% yield by using LHMDS as base. ^{1}H NMR spectra of both the crude and the isolated product showed that the ratios of angelate **4** to tiglate **5** were higher than 99:1. On a 10-g scale preparation, the product was practically free of any tiglate by-product **5** after crystallization and no additional chromatographic purification was necessary (73% yield).

Table 4 Reaction of Angelic Anhydride (**9**)[a] with **2**[b]

Entry	Base	Solvent	Time	Conv. **4/5**[c]	**4/5** ratio[c]
1	–	THF	1 d	–	–
2	pyridine	pyridine	1 d	55%	4:96
3	DMAP	THF	1 d	55%	4:96
4	LHMDS	THF	1 h	>95%	98:2[a]
5	NaHMDS	THF	2 h	>95%	98:2[a]
6	KHMDS	THF	2 h	>90%	98:2[a]

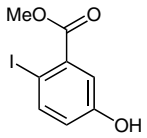
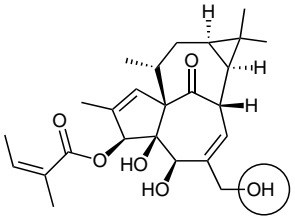
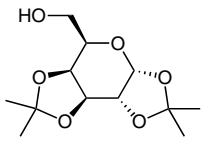
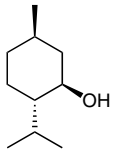
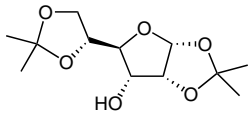
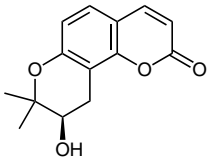
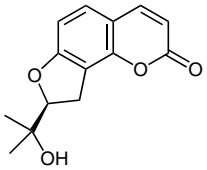
[a] The 98:2 ratio was due to a content of approximately 3% angelic-tiglic mixed anhydride in commercially available angelic anhydride.
[b] Ingenol 5,20-acetonide was dissolved in the appropriate solvent at r.t. For the reactions conducted in the presence of a base, the base (large excess of pyridine, 1.5 equiv DMAP, 1.15 equiv LHMDS, 1.15 equiv NaHMDS, 1.15 equiv KHMDS) was added before the addition of angelic anhydride (1.5 equiv in entries 1–3 and 1.2 equiv in entries 4–6).
[c] Conversions and angelate/tiglate ratios were estimated from ^{1}H NMR of the crude reaction mixtures.

With the optimized conditions for angeloylation of **2** in hand, we investigated the scope of this methodology as a next step. For this purpose, we chose a variety of alcohols, and the results are outlined in Table 5. For phenol and pri-

mary alcohols, we chose Cs_2CO_3 as activating base (Table 5, entries 1–3). The reactions were relatively slow but high-yielding. For secondary alcohols, the stronger base LHMDS was a better choice. The reactions were complete within 30 minutes (Table 5, entries 4–6). Tertiary alcohols required longer reaction times even when LHMDS was used, but the reactions still gave good yields (e.g., Table 5, entry 7).

In the final step of producing **1**, the protecting group in **4** was removed (Scheme 1). For the acidic hydrolysis of acetonide **4**, several of the investigated acids (e.g., HCl, methanesulfonic acid and H_3PO_4) were found suitable. By using HCl–MeOH to remove the protecting group, we observed only minimal isomerization of angelate to tiglate (ratio 99:1). The quantitative formation of **1** concluded the three-step semisynthesis of ingenol 3-angelate (**1**) from ingenol in a total yield of 62%. On a 6-g scale using H_3PO_4, **1** was obtained in 71% yield from **4** after recrystallization with a comparable ratio of angelate to tiglate of 99:1. This larger scale synthesis involving three recrystal-

Table 5 Transformation of Various Alcohols to Angelate Esters by Reaction with Angelic Anhydride (**9**)[a–c]

Entry	Alcohol	Base	Time	Isolated yield (*Z*/*E* ratio)[d]
1[a]		Cs_2CO_3	1 h	96%
2[a]		Cs_2CO_3	1 h	78%
3[a]		Cs_2CO_3	1.5 h	82%
4[b]		LHMDS	10 min	92%
5[b]		LHMDS	30 min	96%
6[b]		LHMDS	10 min	90%
7[b]		LHMDS	60 min	64%

[a] A mixture of angelic anhydride (1.2 equiv), an alcohol (1.0 equiv) and Cs_2CO_3 (1.2 equiv) in MeCN was stirred at r.t. (entries 1–3). The reactions were monitored by TLC.

[b] LHMDS (1.2 equiv) was added to a solution of angelic anhydride (1.2–1.6 equiv) and an alcohol (1 equiv) at r.t. The solution was stirred at the same temperature.

[c] Angelic anhydride was prepared from angelic acid with DCC as coupling reagent and chromatographically purified.

[d] The angelate (*Z*)/tiglate (*E*) ratios were determined by ^{1}H NMR of the isolated product and found to be at least 99:1.

lization steps provided **1** from ingenol in a total yield of 31%.

In summary, through investigating and optimizing the key angeloylation reaction, we can synthesize ingenol 3-angelate on large scale with only minimal isomerization in the last step. We have explored the scope of our stereoconservative angeloylation protocol, which proved to be general and applicable for various types of alcohols. We believe the method of using pure angelic anhydride and a suitable base will find wide use in the future in the preparation of angelate esters, which often are moieties of natural products. However, it should be pointed out that the present method may not be suitable for substrates which do not tolerate strong bases. In those cases, our method cannot replace Beeby's and Greene's methods. We have also discussed a likely mechanism for the cause of the isomerization when using DMAP or pyridine (*cf*. the mechanistic study of the analogous isomerization during reductive amination of 3,3-disubstituted propenals[7]). Even though this isomerization phenomenon has been observed previously,[8c,11] DMAP and pyridine still find use in such reactions.[8d–h,9,12k,l] Thus, we would like to point out that care must be taken when nucleophilic bases like pyridine and DMAP are used on substrates capable of acting as reversible Michael acceptors and also with the interpretation of published experiments under similar conditions.

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