from the directly measured[8] $k_{CH_3}/k_{CD_3} = 0.83 \pm 0.05$ and $k_{12}/k_{13} = 1.09 \pm 0.05$ for the maximal velocity of methylation of 3,4-dihydroxyacetophenone by COMT. The large magnitude of k_{12}/k_{13} here suggests that the S_N2 reaction is fully rate limiting.[8] Assuming equal contributions from each of the three deuteriums (rule of the geometric mean[9]) and the usual relations[10,11] between ^2H and ^3H and ^{13}C and ^{14}C isotope effects, we obtain $k_T/k_{14} = 1.29 \pm 0.12$. This is in good agreement with $J_{ovp} = 1.35 \pm 0.05$ suggesting that, for para methylation of dopamine, the S_N2 step alone determines the overall rate. For the meta pathway, $J_{ovm} = 1.16 \pm 0.07$, much smaller than expected for a pure S_N2 transition state, which indicates that a binding step or conformational change now "dilutes" the isotope effect. When the pH is lowered to 6.2, the S_N2 step slows in relation to the binding step. Then the S_N2 step determines the rate here also ($k_T/k_{14} = 1.32 \pm 0.10$).

Registry No. COMT, 9012-25-3; ^3H, 10028-17-8; ^{14}C, 14762-75-5; dopamine, 51-61-6.

(8) Hegazi, M. F.; Borchardt, R. T.; Schowen, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 4359.
(9) Bigeleisen, J. *J. Chem. Phys.* **1955**, *23*, 2264.
(10) Swain, C. G.; Stivers, E. C.; Reuwer, J. F., Jr.; Schaad, L. J. *J. Am. Chem. Soc.* **1958**, *80*, 5885.
(11) Stern, M. J.; Vogel, P. C. *J. Chem. Phys.* **1971**, 55, 2007.

4,4′,4″-Tris(4,5-dichlorophthalimido)trityl: A New Type of Hydrazine-Labile Group as a Protecting Group of Primary Alcohols

Mitsuo Sekine* and Tsujiaki Hata

Department of Life Chemistry
Tokyo Institute of Technology, Nagatsuta
Midoriku, Yokohama 227, Japan

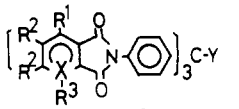
Received May 7, 1984

In the strategy for the synthesis of natural products containing both primary and secondary hydroxyl groups, the former has usually been protected with a trityl or hindered acyl group.[1] However, its selective removal required for further transformations is difficult, when acid- or base-sensitive functions are present in the same molecule. Recently, van Boom[2] has reported the use of hydrazine-labile levulinyl ester as a primary hydroxyl protecting group for oligonucleotide synthesis. However, this group lacks the selectivity in its introduction to primary alcohols of other substrates[3] and has inherent poor lipophilicity.

In this paper, we describe a new trityl-type of primary hydroxyl protecting group, 4,4′,4″-tris(4,5-dichlorophthalimido)trityl (CPTr), which is labile to hydrazine. We considered that 4,4′,4″-triphthalimidotrityl halides, which would be derived from tris(4-aminophenyl)methanol (pararosaniline) and phthalic anhydrides, might be used as tritylating agents to protect primary alcohols in the form of acid-stable trityl ethers owing to the strong inductive effect of the phthalimide groups and that upon hydra-

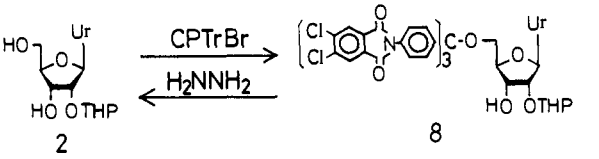
(1) For a comprehensive review, see: Reese, C. B. "Protective Grops in Organic Synthesis"; McOmie, J. F. W., Ed.; Plenum: New York, 1973; pp 95–143. Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981.
(2) (a) van Boom, J. H.; Burgers, P. M. J. *Tetrahedron Lett.* **1976**, 4875. (b) de Rooij, J. F. M.; Eille-Hazelegar, G.; van Deursen, P. H.; Serdijn, J.; J.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 537. (c) den Hartog, J. A. J.; van Boom, J. H. *Ibid.* **1981**, *100* 275. (d) den Hartog, J. A. J.; Wille, G.; van Boom, J. H. *Ibid.* **1981**, *100*, 320.
(3) The levulinations of 2′-*O*-(tetrahydropyran-2-yl)uridine and 2′-*O*-(1,3-benzodithiol-2-yl)uridine[4] by van Boom's method[2d] resulted in the 5′-levulinated products in 50–65% yields. This relatively poor selectivity may be due to the sterically less hindered 2′-*O*-protecting group relative to the 4-methoxy(tetrahydropyran-4-yl) group that has a quaternary carbon bound to the 2′-oxygen.

Chart I



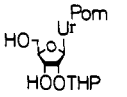
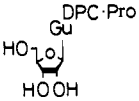
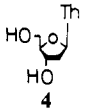
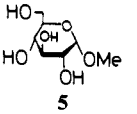
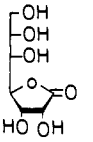
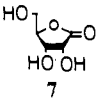
	R^1	R^2	R^3	X	Y
1a:	H	H	H	C	OH
1b:	H	Cl	H	C	OH
1c:	Cl	Cl	H	C	OH
1d:	H	H	–	N	OH
CPTrBr:	H	Cl	H	C	Br

Scheme I



2 8

Table I. Results and Conditions of the Reactions of **2**–**7** with CPTrBr[a,b]

substrate compd	2,6-lutidine, equiv	time, min	primary CPTr ether yield, compds	%
 **2**	2[c]	15	8	84
 **3**	0	15	9	73
 **4**	2	30	10	85
 **5**	2	20	11	75
 **6**	2	20	12	88
 **7**	2	20	13	70

[a] These reactions were carried out at room temperature by using 2 equiv each of CPTrBr and $AgNO_3$ in dimethylformamide (10 mL/(L mmol of the substrate)). [b] In the case of compounds containing an acid-sensitive group, 2,6-lutidine was added prior to addition of CPTrBr. [c] When 2,6-lutidine was eliminated, the THP group was lost to a considerable extent (~15%).

0002-7863/84/1506-5763$01.50/0

zine-mediated dephthaloylation the modified trityl group could be removed via unstable 4,4',4''-triaminotrityl ethers.

Therefore, we synthesized masked pararosaniline derivatives (**1a-d**) in more than 85% yields simply by treatment of pararosaniline with several kinds of phthalic anhydrides in pyridine at 80 °C for 1-2 h followed by addition of acetic anhydride (Chart I). The carbinols **1a-d** were stable under acidic conditions such as 80% acetic acid (room temperature, 24 h), but **1d** decomposed during column chromatography, and the others were stable on silica gel. Expectedly, deacylation of **1a-d** with a 1 M hydrazine solution in pyridine-acetic acid (3:1, v/v) resulted in formation of paparosaline. The order of the deacylations observed is **1b** (t_{comp} = <5 min) ≃ **1d** (<5 min) < **1c** (15 min) << **1a** (10 h).

From these results, we prepared 4,4',4''-tris(4,5-dichlorophthalimido)trityl bromide (CPTrBr) as slightly yellowish crystals (mp > 270 °C) in 82% yield by bromination of **1b** with acetyl bromide in refluxing benzene for 7 h. Because of these simple operations, CPTrBr can be prepared on a kilogram scale.[7] This new reagent allowed facile tritylation with appropriately protected nucleoside derivatives (**2-4**) by the silver ion promoted reaction[8] in the presence of $AgNO_3$ in dimethylformamide to give 5'-tritylated nucleoside derivatives (**8-10**) (Scheme I) in high yields as shown in Table I.[9] The selective introduction of the CPTr group on the primary alcohols of other polyfunctional nucleoside and carbohydrate derivatives (**5-7**) was also achieved in high yields. The CPTr group was found to be stable in pyridine-water (2:1) and even in 80% acetic acid at room temperature for 24 h. Detritylation of compounds **8-10** by use of 1 M hydrazine in pyridine-acetic acid (3:1, v/v)[11] for 20 min followed by quenching with pyridine-acetic acid (1:3, v/v)[12] expectedly led to direct C-O bond fission of the CPTr ethers giving rise to the parent compounds **2-4** quantitatively. It is clearly shown that the N^3-pivaloyloxy)methyl (Pom)[13,14] (for U), O^6-diphenylcarbamoyl (DPC)[16] (for G), N^2-propionyl (Pro)[16] (for G), and 2'-*O*-tetrahydropyran-2-yl (THP)[17] groups (see table I) survived the hydrazine reaction.

Another facinating feature of the CPTr group is that CPTr-containing compounds can be easily detected as red spots on TLC by heating on a hot plate or by spraying 1 M hydrazine in pyridine-acetic acid (3:1, v/v). Its great lipophilicity also helps isolation of the products. CPTr-containing products are more readily eluted from a silica gel column than the DMTr derivatives. Furthermore, the degree of deprotection can be monitored visibly by the color of the liberated pararosaniline. The amount of pararosaniline formed as the result of the hydrazine treatmnet can also be measured spectrophotometrically in a neutral buffer or ethanol by using the ϵ value of 93 000 at 544 nm (λ_{max}) without using strong acids such as perchloric acid.

These results strongly suggest that the CPTr group can be used conveniently in the synthesis of oligoribonucleotides in both the liquid and solid phases. In fact, we achieved high-yield syntheses of several oligoribonucleotides containing the four common ribonucleosides according to our approach.[18] These results will be shortly reported elsewhere. In conclusion, the CPTr group is superior to the levulinyl group in several aspects and will be applicable to the synthesis of a wide variety of natural products.

(4) Sekine, M.; Hata, T. J. *Org. Chem.* **1983**, *48*, 3112.
(5) We also reported a similar 5'-OH protecting group, 4,4',4''-tris(levulinyloxy)trityl.[6] However, this group was removed by the impractical procedure involving successive hydrazinolysis, extraction, and heating in a pyridine-acetic acid medium.[6] Its introducing agent, [4,4'-tris(levulinyloxy)-trityl]carbinol, was isolated only by inconvenient silica gel column chromatography.
(6) Sekine, M.; Hata, T., unpublished results.
(7) 4,5-Dichlorophthalic acid is commercially available from Aldrich Co. Ltd. and is converted quantitatively to the acid anhydride by heating with acetic anhydride in CCl_4.
(8) Ogilvie, K. K.; Cheriyan, U. O.; Radatus, B. K. *Can. J. Chem.* **1982**, *60*, 3005.
(9) The CPTr group can also be introduced onto the 5'-hydroxyls of the other 2'-*O*-tetrahydropyranylribonucleoside derivatives in high yields (unpublished data).
(10) Footnote deleted in proof.
(11) This cleavage mode has been reported by Letsinger et al. (Letsinger, R. L.; Caruthers, M. H.; Miller, P. S.; Ogilvie, K. K. *J. Am. Chem. Soc.* **1967**, *89*, 7146, who first used β-benzoylpropionyl as a hydrazine-labile protecting group in nucleotide chemistry.
(12) This quenching workup is very effective for the complete conversion of the last traces of the intermediates to the parent ribonucleosides.
(13) The Pom group has been used as a protecting group of adenine by: Rasmussen, M.; Leonard, N. J.; *J. Am. Chem. Soc.* **1967**, *8*., 5439.
(14) The anisoyl group has been used for protecting the N^4-amino function of uridine in this lab.[15] However, this was somewhat sensitive to the hydrazine treatment. We found that the Pom group was resistant to hydrazine. The details of this group will be reported elsewhere.
(15) Kamimura, T.; Masegi, T.; Urakami, K.; Honda, S.; Sekine, M.; Hata, T. *Chem. Lett.* **1983**, 1051.
(16) Kamimura, T.; Tsuchiya, M.; Koura, K.; Sekine, M.; Hata, T. *Tetrahedron Lett.* **1983**, *24*, 2775.
(17) Griffin, B. E.; Jarman, M.; Reese, C. B. *Tetrahedron* **1967**, *24*, 639.
(18) Kamimura, T.; Tsuchiya, M.; Urakami, K.; Koura, K.; Sekine, M.; Shinozaki, K.; Miura, K.; Hata, T. *J. Am. Chem. Soc.*, in press.

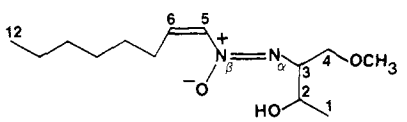
Biosynthesis of Elaiomycin. 2. An Unusual Origin for the (Methoxyamino)butanol Moiety

Ronald J. Parry* and Jay V. Mueller

Department of Chemistry, Rice University
Houston, Texas 77251

Received April 24, 1984

The antibiotic elaiomycin (**1**) is a naturally occurring azoxy compound isolated from the fermentation broth of *Streptomyces gelaticus*.[1] Elaiomycin exhibits novel biological activity since



1

it inhibits axenic multiplication of *Mycobacterium tuberculosis*.[2] The antibiotic has also been found to induce tumors in rats.[3] As a naturally occurring azoxy compound, elaiomycin is a member of a small class of unusual natural products that includes (*p*-carboxyphenyl)azoxy cyanide,[4] the cycad toxins macrozamin and cycasin,[5] and the antifungal agent LL-BH872α.[6] Previous experiments in our laboratory have demonstrated[7] that C-5 to C-12 of elaiomycin and the β-nitrogen atom of the antibiotic are derived from *n*-octylamine. We now report experiments which establish that the (methoxyamino)butanol moiety of the antibiotic is biosynthesized in an unusual manner.

(1) (a) Haskell, T. H.; Ryder, A.; Bartz, Q. R. *Antibiot. Chemother. (Washington, D.C.)* **1954**, *4*, 141. (b) Stevens, C. L.; Gillis, B. T.; French, J. C.; Haskell, T. H. *J. Am. Chem. Soc.* **1956**, *78*, 3229. (c) Stevens, C. L.; Gillis, B. T.; French, J. C.; Haskell, T. H. *Ibid.* **1958**, *80*, 6088. (d) Stevens, C. L.; Gillis, B. T.; Haskell, T. H. *Ibid.* **1959**, *81*, 1435. (e) Taylor, K. G.; Riehl, T. *Ibid.* **1972**, *94*, 250.
(2) (a) Ehrlich, J.; Anderson, L. E.; Coffey, G. L.; Feldman, W. H.; Fisher, M. W.; Hillegas, A. B.; Karlson, A. G.; Kaudsen, M. P.; Weston, J. K.; Youmans, A. S.; Youmans, G. P. *Antibiot. Chemother. (Washington, D.C)* **1954**, *4*, 338. (b) Karlson, A. G. *Ibid.* **1962**, *12*, 446.
(3) Baroni, C. D.; Ward, E. N. *Nature (London)* **1969**, *221*, 765.
(4) Gasco, A.; Serafino, A.; Mortarini, V.; Menziani, E. *Tetrahedron Lett.* **1974**, 3431.
(5) (a) Lythgoe, B.; Riggs, N. V. *J. Chem. Soc.* **1949**, 2716. (b) Langley, B. W.; Lythgoe, B.; Riggs, N. V. *Chem. Ind. (London)* **1951**, 75. (c) Riggs, N. V. *Ibid.* **1956**, 926. (d) Korsch, B.; Riggs, N. V. *Tetrahedron Lett.* **1964**, 523.
(6) (a) McGahren, W. J.; Kunstmann, M. P. *J. Am. Chem. Soc.* **1969**, *91*, 2808. (b) McGahren, W. J.; Kunstmann, M. P. *Ibid.* **1970**, *92*, 1587. (c) McGahren, W. J.; Kunstmann, M. P. *J. Org. Chem.* **1972**, *37*, 902.
(7) Parry, R. J.; Rao, H. S. P.; Mueller, J. *J. Am. Chem. Soc.* **1982**, *104*, 339.

0002-7863/84/1506-5764$01.50/0